CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203567Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 203567 SUPPL # NA HFD # NA

Trade Name Jublia

Generic Name (efinaconazole) topical solution, 10%

Applicant Name Dow Pharmaceutical Sciences

Approval Date, If Known June 20, 2014

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

DPSI-IDP-108-P3-01 and -02: Phase 3 Clinical Trials
DPSI-IDP-108-P3-02 and -02: Phase 3 Clinical Trials

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

DPSI-IDP-108-P3-01 and -02: Phase 3 Clinical Trials
DPSI-IDP-108-P3-02 and -02: Phase 3 Clinical Trials

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # YES ☐ ! NO ☐
! Explain:

Investigation #2 !
!
IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Strother D. Dixon
Title: Regulatory Project Manager
Date: May 16, 2014

Name of Office/Division Director signing form: Stanka Kukich, M.D.
Title: Deputy Director, Division of Dermatology and Dental Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12;

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STROTHER D DIXON
05/19/2014

DAVID L KETTL
05/19/2014

STANKA KUKICH
05/22/2014

1.3.3 Debarment Certification

Debarment Certification

Dow Pharmaceutical Sciences herewith certifies that the services of any persons debarred under Section 306(a) or (b) were not and will not be used in any capacity in conjunction with this application.

Tage Ramakrishna, MD
Chief Medical Officer

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 203567 BLA # NA	NDA Supplement # NA BLA Supplement # NA	If NDA, Efficacy Supplement Type: NA *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Jublia Established/Proper Name: (efinaconazole) Dosage Form: topical solution		Applicant: Dow Pharmaceutical Sciences Agent for Applicant (if applicable): NA
RPM: Strother D. Dixon		Division: Dermatology and Dental Products

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is June 20, 2014	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None CR – May 13, 2013
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other Approval Page & weekly FDA News & Notes
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included 6/2/14
Documentation of consent/non-consent by officers/employees	☒ Included 6/2/14
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Approval 6/6/14; CR May 13, 2013 (no labeling)
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included 6/4/14
• Original applicant-proposed labeling	☒ Included 12/20/13 (resub) 6/26/12 (original)
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☒ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included May 23, 2014
• Original applicant-proposed labeling	☒ Included December 20, 2013 (resub) June 26, 2012 (original)
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included May 16, 2014
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	3/29/14 - Acceptable Letter 3-26-14 - Acceptable Review 4/15/13 - Acceptable Letter 4/12/13 - Acceptable Review 11/9/12 - Not Acceptable Letter 11/9/12 - Not Acceptable Review
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☐ None 4/30/14; 9/25/12 DMEPA: ☐ None 3/14/14, 2/28/13 DMPP/PLT (DRISK): ☐ None 3/31/14, 3/5/2013 (deferral memo) OPDP: ☐ None 3/28/14, 8/2/13 SEALD: ☒ None CSS: ☒ None Other: ☒ None

Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	10/1/12 ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included 5/22/14
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 4/30/14 If PeRC review not necessary, explain: _____	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) *(do not include previous action letters, as these are located elsewhere in package)*	1/30/14 Information Request 12/30/13 Acknowledgement 9/4/13 Verbal Advice 3/8/13 Discipline Review 12/21/12 Information Request 11/20/12 Informaiton Request 10/17/12 MV Materials Received 9/28/12 MV Materials Requested 9/27/12 Filing w/ Issues 8/10/12 Email IR 8/2/12 IR 7/27/12 Acknowledgement
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	11/15/12
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☐ N/A or no mtg 7/17/13
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 4/17/12
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 8/4/09
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	NA

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None 6/5/14, 5/13/13
Division Director Summary Review *(indicate date for each review)*	☐ None 6/2/14, 4/24/13
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 4/16/13
PMR/PMC Development Templates *(indicate total number)*	☐ None 1 - 5/30/14
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☐ No separate review See CDTL
• Clinical review(s) *(indicate date for each review)*	5/16/14 4/15/13
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	4/15/13, p. 13
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	NA NA ☐ None 5/23/14
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested 7/2/13, 7/1/13, 6/10/13, 3/5/13
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None 5/17/14, 3/4/13, 12/8/12 (mid-cycle)
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None 5/05/14, 3/5/13

Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 5/6/14, 3/7/13
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☐ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ No separate review 3/1/13
• Supervisory Review(s) *(indicate date for each review)*	☐ No separate review 3/5/13
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 5/9/14, 3/5/13
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☐ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc 12/6/12
❖ ECAC/CAC report/memo of meeting	☐ None 11/30/12 Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☐ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ No separate review 4/12/13
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 5/29/14, 5/09/14, 1/10/14 filing, 5/10/13 (addendum memo) 4/11/13 (addendum memo), 3/4/13 (addendum memo), 2/8/13
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed 1/13/14
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	CMC Review 2/8/13, p. 50
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	

❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within **2 years** of action date) *(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[5])*	Date completed: 5/27/14 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER (date of most recent TB-EER must be within **30 days** of action date) *(original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☒ Completed ☒ Requested ☐ Not yet requested ☐ Not needed (per review)

[5] i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STROTHER D DIXON
06/09/2014

From:	Dixon, Strother
To:	Humphrey, Sean (SHumphrey@dowpharmsci.com)
Cc:	Gould, Barbara
Subject:	Postmarketing Requirement: NDA 203567 Julia (efinaconazole) topical solution, 10%
Date:	Friday, May 23, 2014 3:15:00 PM

Greetings. Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Julia (efinaconazole) topical solution, 10%. The Agency has identified the following postmarketing requirement study to be conducted post approval:

> A Multicenter, Randomized, Double-Blind Study Evaluating the Safety, Efficacy and Pharmacokinetics of Julia Topical Solution, 10% versus Vehicle in Pediatric Subjects ages 12 to 17 years with Onychomycosis of the Toenails
>
> Final Protocol Submission: September 2014
> Study/Trial Completion: March 2018
> Final Report Submission: September 2018

Please submit to your NDA by Tuesday, May 27, 2014 confirmation of your proposed dates for final protocol submission, study/trial initiation, and final report submission for the required postmarketing study.

If you require additional information or have questions, please do not hesitate to contact me directly.

Regards,
Strother

Strother D. Dixon
Regulatory Health Project Manager
Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food and Drug Administration
E-mail: strother.dixon@fda.hhs.gov
Phone: 301.796.1015
Fax: 301.796.9895

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STROTHER D DIXON
05/23/2014

From:	Dixon, Strother
To:	Humphrey, Sean (SHumphrey@dowpharmsci.com)
Cc:	Gould, Barbara
Subject:	Agency Proposed Labeling: NDA 203567 Jublia (efinaconazole) topical solution, 10%
Date:	Wednesday, May 21, 2014 4:33:00 PM
Attachments:	Agency Proposed Patient Info Labeling NDA 203567 JUBLIA 20140521.doc Agency Proposed Labeling NDA 203567 JUBLIA 20140521.doc

Greetings. Attached, please find the Agency proposed PI and PPI labeling for NDA 203567 Jublia (efinaconazole) topical solution, 10%. Please submit agreed upon labeling to the NDA and provide a courtesy copy of the submission (e.g. labels, 356h and cover letter) to me via email by Friday, May 23, 2014.

Please confirm receipt of this email.

If you require additional information or have questions, please do not hesitate to contact me directly.

Regards,
Strother

Strother D. Dixon
Regulatory Health Project Manager
Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food and Drug Administration
E-mail: strother.dixon@fda.hhs.gov
Phone: 301.796.1015
Fax: 301.796.9895

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STROTHER D DIXON
05/22/2014

PeRC PREA Subcommittee Meeting Minutes
April 30, 2014

PeRC Members Attending:
Lynne Yao
Rosemary Addy
Jane Inglese
Wiley Chambers
Karen Davis-Bruno (only reviewed Contrave)
Peter Starke
Gregory Reaman
Daiva Shetty
Shrikant Pagay
Barbara Buch
Dianne Murphy

Agenda

NDA	(b) (4)		
NDA			
NDA	203567	JUBLIA (efinaconazole) Partial Waiver_Deferral_Plan	Topical treatment of onychomycosis

(b) (4)

(b) (4)

JUBLIA (efinaconazole) Partial Waiver Deferral Plan

- NDA 203567 seeks marketing approval for JUBLIA (efinaconazole) for topical treatment of onychomycosis.
- The application triggers PREA as directed to a new active ingredient.
- The application has a PDUFA a goal date of June 20, 2014.
- *PeRC Recommendations:*
    - The PeRC disagreed with the Division's recommendation to waive studies for pediatric patients less than 12 year of age. The PeRC agreed that the incidence of onychomycosis in pediatric patients is low relative to the incidence in adults. However, the sponsor's own data suggest that there are a small but consistent number of visits each year for this diagnosis in children less than 12. Additionally, there is only one other topical product approved for use in children (penlac) and is it likely that this topical product would be used if approved in children less than 12. Furthermore, the EMA has required studies for topical onychomycosis products down to 2 years of age. Therefore, the PeRC recommended a partial waiver for pediatric patients aged birth to less than 2 years because studies would be impossible or highly impracticable.
    - The PeRC also advised the Division that if efficacy can be extrapolated to pediatric patients less than 12 years of age from adults and pediatric patients greater than 12 years of age, then fewer numbers of patients less than 12 years of age might be needed to establish safety and dosing. Additionally, opening enrollment to younger patients should be strongly considered, but if the sponsor is unable to enroll patients, despite good faith attempts, a waiver could be issued later.
    - The PeRC recommended a deferral for pediatric patients aged 2 to less than 17 years because adult studies have been completed and the product is ready for approval.
    - The Division should consider issuing a WR for this active moiety.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JANE E INGLESE
05/12/2014

From:	Dixon, Strother
To:	Humphrey, Sean (SHumphrey@dowpharmsci.com)
Cc:	Gould, Barbara
Subject:	Agency Proposed Labeling: NDA 203567
Date:	Friday, May 09, 2014 5:11:00 PM
Attachments:	Agency Proposed Labeling NDA 203567 JUBLIA 20140509.doc

Greetings. Attached, please find the Agency proposed labeling for NDA 203567 Jublia (efinaconazole) topical solution, 10%. In addition, please find the Agency's recommendations for carton and container labeling below.

Carton and Container label (all package sizes):

1. The established name is not commensurate to the prominence of the proprietary name as per CFR 201.10(g)(2). Revise the presentation of the proprietary name to use title case (i.e. Jublia) and ensure that the established name is at least ½ the size of the proprietary name and commensurate in prominence to the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features per CFR 201.10(g)(2).
2. The unit of measure for the net quantity statement is presented in the English and metric systems. We find this to be duplicative and it crowds the container labels. Revise the net quantity statement to be presented only in the metric system unit of measure (i.e. mL).

Container label (all package sizes):

3. Insert a comma between dosage form, Solution, and strength, 10%, in the principle display panel.
4. Add the route of administration statement "For topical use Only."
5. Add the following handling instructions:
    a. Protect from freezing
    b. Flammable; keep away from heat or flame

Carton label (all package sizes):

6. Insert a comma between dosage form, Solution, and strength, 10%, in the principle display panel and throughout the running text.
7. Revise (b) (4) to "anhydrous citric acid."
8. Revise (b) (4) to "For Topical Use Only" in bold font and using larger font size than in the statement "Not for use in the eyes".
9. Add the following handling instructions:
    a. Protect from freezing
    b. Keep bottle tightly closed
    c. Store in upright position
10. Revise the storage temperature statement to read " Store at 20°C-25°C (68°F-77°F); excursions permitted 15°C to 30°C."
11. Revise the usual dosage statement to read "Apply to affected toenail(s) once daily. See package insert for full Prescribing Information." As currently presented (b) (4) .

12. Relocate the statement “Keep away from children” to appear below the related cautionary statement “Important: This package is not child-resistant”. (b) (4) [redacted]

Please submit agreed upon labeling to the NDA and provide a courtesy copy of the submission (e.g. label, 356h and cover letter) to me via email by Thursday, May 15, 2014.

Please confirm receipt of this email.

If you require additional information or have questions, please do not hesitate to contact me directly.

Regards,
Strother

Strother D. Dixon
Regulatory Health Project Manager
Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food and Drug Administration
E-mail: strother.dixon@fda.hhs.gov
Phone: 301.796.1015
Fax: 301.796.9895

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STROTHER D DIXON
05/09/2014

Dear Review Division:

The attached template includes the necessary documentation to facilitate the *required* Pediatric Review Committee (PeRC) review of Waivers, Deferrals, Pediatric Plans, and Pediatric Assessments before product approval.

Complete the section(s) of this template that are relevant to your *current submission.*

Definitions:

Deferral *– A deferral is granted when a pediatric assessment is required but has not been completed at the time the New Drug Application (NDA), Biologics License Application (BLA), or supplemental NDA or BLA is ready for approval. On its own initiative or at the request of an applicant, FDA may defer the submission of some or all required pediatric studies until a specified date after approval of the drug or issuance of the license for a biological product if the Agency finds that the drug or biological product is ready for approval in adults before the pediatric studies are completed, the pediatric studies should be delayed until additional safety and effectiveness data have been collected, or there is another appropriate reason for deferral.*

Full Waiver *– On its own initiative or at the request of an applicant, FDA may waive the requirement for a pediatric assessment for all pediatric age groups if: (1) studies would be impossible or highly impracticable; (2) there is evidence strongly suggesting that the product would be ineffective or unsafe in all pediatric age groups; or (3) the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, AND is not likely to be used in a substantial number of pediatric patients. If studies are being waived because there is evidence that the product would be ineffective or unsafe in all pediatric age groups, this information MUST be included in the pediatric use section of labeling.*

Partial Waiver *– FDA may waive the requirement for a pediatric assessment for a specific pediatric age group if any of the criteria for a full waiver are met for that age group or if the applicant can demonstrate that reasonable attempts to produce a pediatric formulation for that age group have failed. If a partial waiver is granted because a pediatric formulation cannot be developed, the partial waiver will only cover the pediatric groups requiring that formulation.*

Pediatric Assessment *– The pediatric assessment contains data gathered from pediatric studies using appropriate formulations for each age group for which the assessment is required. It also includes data that are adequate to: (1) assess the safety and effectiveness*

of the product for the claimed indications in all relevant pediatric subpopulations; and (2) support dosing and administration for each pediatric subpopulation for which the data support a finding that the product is safe and effective.

***Pediatric Plan** – A pediatric plan is the applicant's statement of intent describing the planned or ongoing pediatric studies (e.g., pharmacokinetics/pharmacodynamics, safety, efficacy) that they plan to conduct or are conducting (i.e., the pediatric studies that will comprise the pediatric assessment). If necessary, the plan should address the development of an age-appropriate formulation and must contain a timeline for the completion of studies. FDA recommends that the timeline should include the dates the applicant will: (1) submit the protocol; (2) complete the studies; and 3) submit the study reports.*

***Pediatric Population/Patient**- 21 CFR 201.57 defines pediatric population (s) and pediatric patient (s) as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.*

***PREA Pediatric Record/Pediatric Page** – The pediatric record is completed for all NDAs, BLAs, or supplemental NDAs or BLAs. This record indicates whether the application triggers the Pediatric Research Equity Act (PREA), and if so, indicates how pediatric studies will be or have been addressed for each pediatric age group. If the Agency is waiving or deferring any or all pediatric studies, the pediatric record also includes the reason(s) for the waiver and/or deferral. (Note that with the implementation of DARRTS, the Pediatric Record is replacing the Pediatric Page for NDAs. The Pediatric Page is still to be used for BLAs.) For NDAs, the information should be entered into DARRTS and then the form should be created and submitted along with other required PeRC materials. Divisions should complete the Pediatric Page for NDAs that do not trigger PREA and submit the Pediatric Page via email to CDER PMHS until further notice.*

Pediatric Research Equity Act (PREA) Waiver Request, Deferral Request/Pediatric Plan and Assessment Template(s)

BACKGROUND
Please check all that apply: ☐ **Full Waiver** ☒ **Partial Waiver** ☐ **Pediatric Assessment** ☐ **Deferral/Pediatric Plan**

BLA/NDA#: 203567

PRODUCT PROPRIETARY NAME: ESTABLISHED/GENERIC NAME: JUBLIA/efinaconazole solution 10%

APPLICANT/SPONSOR: Dow Pharmaceutical Sciences

PREVIOUSLY APPROVED INDICATION/S:
(1) _None_____
(2) _____
(3) _____
(4) _____

PROPOSED INDICATION/S:
(1) Topical treatment of onychomycosis_____
(2) _____
(3) _____
(4) _____

BLA/NDA STAMP DATE: December 20, 2013

PDUFA GOAL DATE: June 20, 2014

SUPPLEMENT TYPE: Resubmission after CR

SUPPLEMENT NUMBER: Class 2

Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

NEW ☒ active ingredient(s) (includes new combination); ☒ indication(s); ☒ dosage form; ☒ dosing regimen; or ☒ route of administration?

Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication? (Please note, Written Requests may include approved and unapproved indications and may apply to the entire moiety, not just this product.)

Yes ☒ No ☐

Is this application in response to a PREA (Postmarketing Requirement) PMR? Yes ☐ No ☒

If Yes, PMR #_____ NDA #_____

Does the division agree that this is a complete response to the PMR? Yes ☐ No ☒

If Yes, to either question Please complete the Pediatric Assessment Template.

If No, complete all appropriate portions of the template, including the assessment template if the division believes this application constitutes an assessment for any particular age group.

WAIVER REQUEST

Please attach:

☐ ***Draft Labeling (If Waiving for Safety and/or Efficacy) from the sponsor unless the Division plans to change. If changing the sponsor's proposed language, include the appropriate language under Question 4 in this form.***

☐ ***Pediatric Record***

1. Pediatric age group(s) to be waived. Pediatrics age 0 to 11 years, 11 months.

2. Reason(s) for waiving pediatric assessment requirements (***Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for <u>each</u> age group or indication. This section should reflect the Division's thinking.***)

   ☐ Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). (Please note that in the DARRTS record, this reason is captured as "Not Feasible.") If applicable, chose from adult-related conditions on the next page

   ☐ The product would be ineffective and/or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information MUST be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. The language must be included in section 8.4 and describe the safety or efficacy concerns in detail.

   ☒ The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **<u>and</u>** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.

   ☐ Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to support this claim for review by the Division, and this data will be publicly posted***. (This reason is for Partial Waivers Only)***

3. Provide justification for Waiver:

The Division has reviewed recent literature regarding incidence and/or prevalence of onychomycosis in the pediatric population. There appears to be few, if any, cases of onychomycosis in subjects under 12 years of age in the general population. Although some reports suggest higher incidence in the Japanese or Icelandic populations, most pertinent literature shows few pediatric onychomycosis in North America.

4. Provide language Review Division is proposing for Section 8.4 of the label if different from sponsor's proposed language:

See sponsor proposed language in section 8.4. Labeling negotiations are still on going.

Adult-Related Conditions that do not occur in pediatrics and qualify for a waiver

These conditions qualify for waiver because studies would be impossible or highly impractical

Age-related macular degeneration	Cancer:
Alzheimer's disease	Basal cell
Amyotrophic lateral sclerosis	Bladder
Atherosclerotic cardiovascular disease	Breast
Benign Prostatic Hyperplasia	Cervical
Chronic Obstructive Pulmonary Disease	Colorectal
Erectile Dysfunction	Endometrial
Infertility	Gastric
Menopausal and perimenopausal disorders	Hairy cell leukemia
Organic amnesic syndrome	Lung (small & non-small cell)
(not caused by alcohol or other psychoactive substances)	Multiple myeloma
Osteoarthritis	Oropharynx (squamous cell)
Parkinson's disease	Ovarian (non-germ cell)
Postmenopausal Osteoporosis	Pancreatic
Vascular dementia/ Vascular cognitive disorder/impairment	Prostate
Actinic Keratosis	Renal cell

Uterine

DEFERRAL REQUEST

Please attach:

☒ ***Pediatric Record***

1. **Age groups included in the deferral request: 12 years to 18 years of age**

2. **Where deferral is only requested for certain age groups, reason(s) for not including entire pediatric population in deferral request:**

3. **Reason/s for requesting deferral of pediatric studies in pediatric patients with disease:** (***Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for <u>each</u> age group or indication. This section should reflect the Division's thinking.***)

   a. Adult studies are completed and ready for approval
   b. Additional safety or effectiveness data needed (**describe**)
   c. Other (**specify**)

4. **Provide projected date for the submission of the pediatric assessment (deferral date): September 2014**

5. **Did applicant provide certification of grounds for deferring assessments?** ☒ **Yes** ☐ **No**

6. **Did applicant provide evidence that studies will be done with due diligence and at the earliest possible time?** ☒ **Yes** ☐ **No**

SPONSOR'S PROPOSED PEDIATRIC PLAN

1. **Has a pediatric plan been submitted to the Agency?** ☒ **Yes** ☐ **No**

2. Does the division agree with the sponsor's plan? ☒ **Yes** ☐ **No**

3. **Did the sponsor submit a timeline for the completion of studies (must include at least dates for protocol submission, study completion and studies submitted)?** ☒ **Yes** ☐ **No**

a. **Protocol Submission: September 2014**
b. **Study Completion: March 2018**
c. **Study Submission: September 2018**

4. **Has a Written Request been issued? ☐ Yes ☒ No (If yes and the WR matches the proposed pediatric plan, please attach a copy. It is not necessary to complete the remainder of this document)**

5. **Has a PPSR been submitted? ☐ Yes ☒ No (If yes, you may submit a draft WR and have PeRC review WR and deferral/plan at the same time.)**

Please note that the remainder of this section should be completed based on what the Division is requiring regardless of what the sponsor is proposing.

DIVISION'S PROPOSED PK, SAFTEY, AND EFFICACY TRIAL

Please complete as much of the information below as possible. Please note that the portions of the document that are shaded are not required for early stage pediatric plans but are useful if available.

Types of Studies/Study Design: Phase 4, two-arm, study in subjects 12 10 17 years of age.

Nonclinical Studies:

Clinical Studies:
A Multi-center, Randomized, Double-Blind Study Evaluating the Safety and Efficacy of IDP-108 Topical Solution versus Vehicle in Pediatric Subjects with Mild to Moderate Onychomycosis of the Toenails. (DPSI-IDP-108-P3-03)

Age group and population (indication) in which study will be performed:
This section should list the age group and population exactly as it is in the plan.
The objective of this study is to evaluate the safety and efficacy of once daily topically administered IDP-108 for 24 weeks compared with Vehicle in the treatment of pediatric subjects (12 to 17 years of age) with mild to moderate onychomycosis of the toenails.

Number of patients to be studied or power of study to be achieved:
75 subjects randomized 4:1

Entry criteria:

1. *Male or female subject of any race, 12 to 17 years of age (inclusive)*
2. *Clinically diagnosed distal lateral subungual onychomycosis of at least one great toenail (the"target toenail") at the Screening and Baseline Visits, with no more than six toenails and no fingernails involved*
3. *Presence of mild to moderate onychomycosis, defined as 20% to 50% of the area of the clinically affected target toenail involved (as determined by the investigator), without dermatophytomas or lunula (matrix) involvement, at the Screening and Baseline Visits*
4. *Presence of at least 3 mm of clear (uninfected) toenail proximally on the target toenail at the Screening and Baseline Visits*
5. *Have a positive KOH examination at the investigational center of the target toenail within 42 days prior to the Baseline (Day 0) Visit*
6. *Have a positive dermatophyte culture or positive mixed dermatophyte/Candida culture (at the central mycology laboratory) from the target toenail within 42 days prior to the Baseline (Day 0) Visit*

Exclusion:

1. *Presence of severe moccasin tinea pedis at the Screening or Baseline Visits, as determined by the investigator (if inter-digital tinea pedis requires treatment during the study, the subject must agree to use only an investigator-approved topical antifungal therapy)*
2. *Presence of any underlying disease that, in the opinion of the investigator, could present a safety concern for the subject by participating in the study*

Clinical endpoints:

The efficacy variables collected in this study include the microscopic KOH examination and mycological culture outcomes of the target toenail, target toenail assessments and measurements including percent of involvement of the target toenail and toenail growth, non-target toenail assessments, and responses from subjects who native language with English to the quality of life questionnaire. Close-up photographs of the subject's target toenail will be obtained at Baseline, Weeks 12, 24, and 28. These photographs will be used for documentation purposes only, and will not be used for determinations of eligibility, efficacy, or any study-related activities.

Timing of assessments:

Duration of treatment: 24 weeks, Assessments will be Weeks 4, 8, 12, 16, 20, 24 and 28

Statistical information (statistical analyses of the data to be performed):

The primary efficacy endpoint is Complete Cure at Week 28. Complete cure is defined as 0% clinical involvement of the target toenail (toenail is totally clear) in addition to a negative KOH examination and a negative fungal culture of the target toenail sample.
Division comments on product safety: *Are there any safety concerns currently being assessed?* ☐ **Yes** ☒ **No** *Are there safety concerns that require us to review post-marketing safety data before fully designing the pediatric studies?* ☐ **Yes** ☒ **No** *Will a DSMB be required?* ☐ **Yes** ☒ **No** *Other comments:*
Division comments on product efficacy:
Division comments on sponsor proposal to satisfy PREA:

PeRC ASSESSMENT TEMPLATE

Please attach:

☐ ***Proposed Labeling from the sponsor unless the Division plans to change. If changing the language, include the appropriate language at the end of this form.***

☐ ***Pediatric Record***

Date of PREA PMR:
Description of PREA PMR: ***(Description from the PMC database is acceptable)***

Was Plan Reviewed by PeRC? ☐ **Yes** ☐ **No** If yes, did sponsor follow plan?

If studies were submitted in response to the Written Request (WR), provide the annotated WR in lieu of completing the remainder of the Pediatric Assessment template.

Indication(s) that were studied:
This section should list the indication(s) exactly as written in the *protocols.*

Example:
DRUG for the treatment of the signs and symptoms of disease x.

Number of Centers _____

Number and Names of Countries _____

Drug information:

Examples in italics

- **Route of administration**: *Oral*
- ***Formulation:** *disintegrating tablet*
- **Dosage:** *75 and 50 mg*
- **Regimen:** *list frequency of dosage administration*

**If the dosage form is powder for oral suspension; provide information on storage statement and concentration after reconstitution (e.g. with water, juice or apple sauce etc.)*

Types of Studies/ Study Design:
Example:
Study 1: Multi- center, randomized, active controlled double blind study to evaluate the safety and efficacy of (drug name, concentration, form etc) DRUG administered twice daily for the treatment of patients with disease x.
Study 2: PK and safety study of (drug name, concentration, form etc) DRUG in patients with disease x.

Age group and population in which study/ies was/were performed:

Example:
Study 1: patients aged X to Y years.
Study 2: sufficient number of patients to adequately characterize the pharmacokinetics in the above age groups.

Number of patients studied or power of study achieved:
Example:
Study 1: X patients in each treatment arm and was powered to show that (drug name, concentration, form etc) DRUG is not inferior to the active comparator. 50% were females and 25% were less than 3 years.

Study 2: powered and structured to detect a 30% change in (drug name, concentration, form etc) DRUG clearance and other relevant pharmacokinetic parameters. The study included at least X evaluable patients. .

Entry criteria:
This section should list pertinent inclusion/exclusion criteria.

Example:
Entry criteria: Pediatric patients with disease x diagnosed with laboratory test of LFTs
Patients had a negative pregnancy test if female.

Clinical endpoints: *Example:* *Study 1: Clinical outcome and safety were the primary endpoints.* *Study 2: The primary pharmacokinetic analysis of (drug name, concentration, form etc) DRUG attempted to include all the patients in the study with determination of the following parameters: single dose and steady state AUC, Cmax, Tmax, and CL/F*
Statistical information (statistical analyses of the data performed): This section should list the statistical tests conducted. *Example:* *Study 1 - two-sided 95% confidence interval (CI) of treatment difference in improvement rates were within 25% of the control's response rate.* *Study 2: descriptive statistical methods for AUC, C max, Tmax, Cl/F and compared to adults.*
Timing of assessments: *Example:* *Baseline, week 2, week, 6, and end of treatment*

Division comments and conclusions (Summary of Safety and Efficacy)
Provide language Review Division is proposing for the appropriate sections of the label if different from sponsor-proposed language.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STROTHER D DIXON
04/16/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 203567

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Dow Pharmaceutical Sciences
1330 Redwood Way
Petaluma, CA 94954

ATTENTION: Sean Humphrey
Manager, Regulatory Affairs

Dear Mr. Humphrey:

Please refer to your New Drug Application (NDA) dated July 25, 2012, received July 26, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Efinaconazole Topical Solution, 10%.

We also refer to:

- Your Class 2 resubmission, dated and received December 20, 2013
- Our email dated January 30, 2014, sent to you requesting resubmission of your proprietary name as part of the Class 2 Complete Response
- Your correspondence, dated and received February 04, 2014, requesting review of your proposed proprietary name, Jublia

We have completed our review of the proposed proprietary name, Jublia and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your February 4, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Teena Thomas, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0549. For any other information regarding this application, contact Strother Dixon, Regulatory Project Manager in the Office of New Drugs at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
03/29/2014

From:	Thomas, Teena
To:	"shumphrey@dowpharmsci.com"
Cc:	Thomas, Teena
Subject:	PN for NDA 203567
Date:	Thursday, January 30, 2014 7:09:00 AM

Hi Humphrey,

This is regarding NDA 203567 for Efinaconazole (Topical). The proposed name “Jublia” was Granted on 4/15/13 but the NDA received a CR on 5/13/13. You have resubmitted the application (after the CR) for review of labeling for “Jublia” but not submitted a proprietary name. Please note that you need to resubmit the proprietary name even though it was accepted earlier since the original application was a CR. We advise you to resubmit the proprietary name as soon as possible if you intend to do so. Please note that the review division needs 90 days to review the name and if the name is not submitted on time the NDA could be approved without a Proprietary Name. Let me know If you have any questions.

Thanks

,

Teena

Teena Thomas, Pharm.D, CGP
Safety Regulatory Project
Manager FDA, CDER
Office of Surveillance and Epidemiology
Bldg.22, Room 3461
10903 New Hampshire Ave.
Silver Spring, Maryland 20993-0002

Tel: 301.796.0549
E-mail : teena.thomas@fda.hhs.gov

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TEENA THOMAS
03/20/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203567

ACKNOWLEDGE –
CLASS 2 RESUBMISSION

Dow Pharmaceutical Sciences, Inc.
Attention: Sean Humphrey
Manager, Regulatory Affairs
1330 Redwood Way
Petaluma, CA 94954

Dear Mr. Humphrey:

We acknowledge receipt on December 20, 2013, of your December 19, 2013, resubmission to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (efinaconazole) topical solution, 10%.

We consider this a complete, class 2 response to our May 13, 2013 action letter. Therefore, the user fee goal date is June 20, 2014.

If you have any questions, call me at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

Strother D. Dixon
Regulatory Project Manager
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STROTHER D DIXON
12/30/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203567

MEETING MINUTES

Dow Pharmaceutical Sciences
Attention: Sean Humphrey, MS
Manager, Regulatory Affairs
1330 Redwood Way
Petaluma, CA 94954

Dear Mr. Humphrey:

Please refer to your New Drug Application (NDA) dated July 25, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (efinaconazole) Topical Solution, 10%.

We also refer to the meeting between representatives of your firm and the FDA on July 17, 2013. The purpose of the meeting was to discuss the deficiencies outlined in the Complete Response Letter dated May 13, 2013 and the steps needed to address these issues for (efinaconazole) Topical Solution, 10%.

A copy of the official minutes of the meeting and a document you distributed at the meeting (see Attachment 1) are enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Strother D. Dixon, Regulatory Project Manager at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

Stanka Kukich, M.D.
Deputy Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
Attachment 1

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type A
Meeting Category:	Post Complete Response Action
Meeting Date and Time:	July 17, 2013, 11:00 AM
Meeting Location:	FDA White Oak, Bldg 22
Application Number:	NDA 203567
Product Name:	(efinaconazole) Topical Solution, 10%
Proposed Indication:	Topical treatment of onychomycosis
Sponsor/Applicant Name:	Dow Pharmaceutical Sciences
Meeting Chair:	Stanka Kukich, M.D.
Meeting Recorder:	Strother D. Dixon

FDA ATTENDEES
Julie Beitz, M.D., Director, ODE III
Victoria Kusiak, M.D., Deputy Director, ODE III
Stanka Kukich, M.D., Deputy Director, DDDP
David Kettl, M.D., Clinical Team Leader, DDDP
Gary Chiang, M.D., M.P.H., Clinical Reviewer, DDDP
Moo-Jhong Rhee, Ph.D., Branch Chief, DNDQA II, Branch IV
Shulin Ding, Ph.D., Pharmaceutical Assessment Lead, DNDQA II
Bogdan Kurtyka, Ph.D., Product Quality Reviewer, DNDQA II, Branch IV
Matthew E. White, Regulatory Health Project Manager, DDDP
Strother D. Dixon, Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES
Susan Hall, Global Head R&D
(b) (4)
Steven Knapp, Vice President Regulatory Affairs
Steven Koepke, President SRK Consulting, LLC
David Lust, Senior Director, Regulatory Affairs
Tage Ramakrishna, Chief Medical Officer
Pramod Sarpotdar, Executive Director Formulation and Process Development
J. Michael Pearson, Chairman and CEO
Radhakrishnan Pillai, Head Dermatology Development
R. Sean Humphrey, Manager, Regulatory Affairs
Howard B. Schiller, Executive Vice President and Chief Financial Officer

Purpose of the Meeting:
To discuss the deficiencies outlined in the Complete Response Letter dated May 13, 2013 and the steps needed to address these issues for (efinaconazole) Topical Solution, 10%.

Regulatory Correspondence History

We have had the following teleconferences with you:
- March 20, 2013
- March 12, 2013
- October 4, 2012

We have sent the following correspondences:
- May 13, 2013 – Complete Response
- March 8, 2013 – Discipline Review
- December 21, 2012 – Information Request
- December 14, 2012 – (E)CAC Final Report
- November 20, 2012 – Information Request
- November 9, 2012 – Proprietary Denied
- September 28, 2012 – Methods Validation Request
- September 27, 2012 – Filing Communication
- August 10, 2012 – Information Request
- August 2, 2012 –Information Request

Chemistry, Manufacturing and Controls (CMC)

We have carefully reviewed the information provided in the briefing package. Below is our understanding of your proposed preliminary control strategy to address the deficiencies outlined in the Complete Response Letter dated May 13, 2013:

1. Improvement in filling/capping operation by using (b) (4) (b) (4)
2. Detection and rejection of units with leakage/residue prior to batch releas (b) (4) (b) (4)
3. Increase in sample size of weight loss test to 100 units.
4. Inclusion of a shelf-life acceptance criterion for leakage/residue test in drug product specification.

The following are the Agency's responses to your questions based on the preliminary control strategy described above:

Question 1:
Does the FDA agree with the proposed scale of the registration batches relative to planned commercial scale?

Response:
Yes, the proposed scale of the registration batches is acceptable, provided that the registration batches are manufactured using the commercial process with the proposed control strategy. Furthermore, each batch should be tested for all attributes listed in the in-process controls and drug product release/stability specifications.

Question 2:
Does the FDA agree that 1) a new, unique non-visual leakage detection method is not necessary, 2) the addition of a "WIP"(described as the storage of all bottles in horizontal position 2 weeks and (b) (4) (b) (4) and 3) a shelf-life specification for number of bottles with product leakage/residue of NMT (b) (4) similar to that described by USP <771>, is acceptable for this product?

Response:
1. We agree, provided that you can demonstrate that your control strategy can effectively identify and eliminate leaky units, and the released batches can consistently meet the shelf-life drug product specification.

2. We do not agree (b) (4) (b) (4) You may refer to the leakage/residue test results obtained from the in-process testing (i.e., the two 100% visual inspections), and include the results in the certificate of analysis of the batch at the time of batch release. Additionally, those batches with an unusually high number of rejected units due to leakage/residue should undergo additional evaluation (e.g., placed on stability) before release to the market. In other words, we recommend that you should set a limit for the in-process testing on leakage/residue.

Meeting Discussion:
The sponsor agreed to the following:

1. Include the leakage test in the drug product release specification with reference to the (b) (4) and also include the results from the two 100% visual inspections in the certificate of analysis for batch release;

2. Set an action limit in the (b) (4) for the leakage test for batch release;

3. If the batch failed the action limit for batch release, it will be placed on stability.

The Agency stated that the acceptability of the proposed limit of no more than (b) (4) can not be decided prior to review of the data from the registration stability batches.

The sponsor confirmed that during WIP the bottles are to be stored in the controlled room conditions.

3. We do not have adequate information to make a decision regarding the shelf-life acceptance criterion (a) for the leakage/residue test. We are unclear about the details of the proposed method and evaluation criteria. Is weight loss a part of this leakage/residue testing? What are the specific defects included in the evaluation of leakage/residue? Do you propose the same limit to be applied to both major and minor defects? We are concerned with various issues (such as smearing of label, accidental exposure, formulation in the bottle below the declared weight, etc.) associated with leakage/residue.

Meeting Discussion:
The sponsor stated that they would revise 3 separate time-point leakage observations to a single time-point observation.

The Agency recommended that stability units for leakage testing should be placed horizontally to improve the method sensitivity. The sponsor stated that the registration stability studies will have both horizontal and upright orientations, but the post-approval stability protocol was to have only upright orientation. However, based on the Agency's recommendation, the samples for the post approval leakage testing will be placed horizontally.

The Agency recommended the sponsor capture defect information (i.e., major and minor defects) in the registration stability study. The sponsor accepted the Agency's recommendation. The Agency stated that major defects should have a lower tolerance than minor defects.

Question 3:
Does FDA agree that the measures the Sponsor proposes to implement and the data we plan to generate should demonstrate that we have established an appropriately robust control strategy to minimize and detect leakage and residue?

Response:
We will review the data/information provided in the resubmission to determine whether the proposed control strategy can minimize and detect leakage/residue. We expect that the resubmission should include three registration batches with 12 months of long term and 6 months of accelerated stability data for each batch. The batches should be manufactured using the commercial process with the proposed control strategy, and each batch should be tested for all attributes listed in the in-process control and drug product release/stability specifications.

Meeting Discussion:
At the time of resubmission, the sponsor proposed to submit (b) (4) (b) (4) However, the Agency did not find this proposal acceptable.

To support the above proposal, the sponsor proposed to provide additional information. The information will include a side-by-side comparison of supporting batches 1461 and 1494 with the registration batches and technical details on changes in capping procedure that result in higher removal torque. The information will be submitted as a general correspondence to the NDA. The sponsor agreed to include actual available data from the registration batches in this correspondence. The Agency will review the correspondence and make a decision regarding the amount of stability data that the sponsor should include in the resubmission.

The Agency emphasized that the application should be complete at the time of resubmission.

Question 4:
Does FDA concur that Sponsor does not need to repeat the in-use stability testing?

Response:
We agree that the in-use stability testing does not need to be repeated.

Question 5:
Does the FDA agree with the Sponsor's proposed level of stability data to be included in the re-submission?

Response:
We do not agree with the proposed level of stability data.

Batches 1461 and 1494 were not manufactured using the proposed control strategy (e.g. different (b) (4) to be used in the commercial process); therefore, they are not considered to be registration stability batches. Batches 1554 and 788-G appear to be manufactured using the commercial process; therefore, they may be considered to be registration stability batches for the resubmission provided that they have been tested for all attributes listed in the in-process controls and drug product release/stability specifications. See response to Questions 1 and 3.

Question 6:
Does the FDA agree that, pending satisfactory data review of the re-submission, this amount of stability data should be sufficient to enable a conclusion of a (b) (4) month shelf life?

Response:
The expiration dating period to be granted will be determined based on the review of the stability data in the resubmission.

Question 7:
Does FDA agree (b) (4)
(b) (4)
(b) (4)

Response:
No, we do not agree. (b) (4)

(b) (4)

Administrative Comments

Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the NDA might identify additional comments or information requests.

Attachment 1

Regarding FDA's Response 2 to Sponsor's Question 2:

- With regard to the release specification: [redacted]
- With regard to the in-process alert limit: [redacted]
    - The alert limit will be adjusted as appropriate during the validation process.

Does FDA agree with this approach?

Regarding FDA's Response 3 to Sponsor's Question 2:

- Currently during stability, a leaking bottle is defined as [redacted]
- For the visual inspection, [redacted]
- We are not differentiating between major and minor defects (all are added to make the total).
- We propose a specification of NMT [redacted] of total number of leaking units after WIP.

Does FDA agree with this approach?

Regarding FDA's Response to Sponsor's Questions 5 and 3:

- FDA has requested 12 months long-term and 6 months accelerated stability on 3 registration batches.
- In response to FDA's request for the stability data for NDA resubmission, we propose to (b) (4) (b) (4)

The data from batches 1461 and 1494 (b) (4) (b) (4) (b) (4) It should be noted that the chemical integrity of the product on stability has been comparable across all batches manufactured to date and has shown no adverse stability trends. (b) (4) (b) (4)

We seek FDA's concurrence to submit the proposed stability data package in the NDA resubmission.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STANKA KUKICH
08/05/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 203567

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Dow Pharmaceutical Sciences
1330 Redwood Way
Petaluma, CA 94954-7121

ATTENTION: Charity Abelardo, RAC
Acting Senior Director, Regulatory Affairs

Dear Ms. Abelardo:

Please refer to your New Drug Application dated July 25, 2012, received July 26, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Efinaconazole Topical Solution, 10%.

We also refer to your January 17, 2013, correspondence, received January 18, 2013, requesting review of your proposed proprietary name, Jublia. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

The proposed proprietary name, Jublia, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your January 17, 2013 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Janet Anderson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0675. For any other information regarding this application contact Strother Dixon, Regulatory Project Manager in the Office of New Drugs (OND), at (301) 796-1015.

Sincerely,
{See appended electronic signature page}
Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CAROL A HOLQUIST
04/15/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203567

DISCIPLINE REVIEW LETTER

Dow Pharmaceutical Sciences
Attention: Charity Abelardo, RAC
Acting Sr. Director, Regulatory Affairs
1330 Redwood Way
Petaluma, CA 94954

Dear Ms. Abelardo:

Please refer to your July 26, 2012 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (efinaconazole) Topical Solution, 10%.

We also refer to your amendments dated August 6, 10, and 20, September 26, October 17 and 22, December 6, 7, 14, and 21, 2012; and January 9, 2013.

Our review of the Chemistry, Manufacturing and Controls section of your submission is complete, and we have identified the following deficiencies:

1. Inadequate manufacturing process and control information:
   - Details of the process/control are not provided.
   - The submitted information indicated that the filling/packaging operation is incomplete and still evolving.

2. Inadequate specification for the drug product:
   - The currently proposed package integrity test (b) (4) is inadequate and is not capable of ensuring timely detection of leaks.

3. Inadequate integrity of the container/closure system, as evidenced by a high number of leaks observed.

4. Inadequate stability data:
   - The data were obtained from batches manufactured utilizing a non-optimized process.

We have determined that the identified deficiencies preclude discussion of labeling changes and/or postmarketing requirements/commitments at this time.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final

decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, contact Barbara Gould, Chief, Project Management Staff, at (301) 796-4224.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Branch Chief, Branch IV
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MOO JHONG RHEE
03/08/2013
Chief, Branch IV

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203567 **INFORMATION REQUEST**

Dow Pharmaceutical Sciences
Attention: Charity Abelardo, RAC
Acting Sr. Director, Regulatory Affairs
1330 Redwood Way
Petaluma, CA 94954

Dear Ms. Abelardo:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (efinaconazole) Topical Solution, 10%.

We are reviewing the Quality section of your submission and have the following information requests. We request a prompt written response by January 9, 2013 in order to continue our evaluation of your NDA.

1. As communicated in the IR dated Nov. 20, 2012, we continue to be concerned with the package integrity issues.
    a. Provide assessments of drug concentration in the formulation inside leaky bottles that have been stored (b) (4) to verify the drug concentration.
    b. Provide the assessment for bottles with highest leakage for pivotal clinical and registration stability batches.
    c. When providing the drug concentration data, include information regarding the age of the sample, storage condition, Batch #, the degree of leakage, and other testing results (e.g. alcohol content, weight loss, degradants, MLT, etc. if available).
    d. If the age of tested products is greater than 30 months, also provide data from a set of non-leaked bottles of a similar age for comparison.

2. Clarify if the drug product used in the maximal use PK trial (DPSI-IDP-108-P1-03) showed evidence of leakage or known to have leaked. If there was evidence of leakage, provide the degree of leakage.

If you have any questions, contact Strother D. Dixon, Regulatory Project Manager, at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

David Kettl, MD
Clinical Team Leader
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DAVID L KETTL
12/21/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203567

(E) CAC – FINAL REPORT

Dow Pharmaceutical Sciences
Attention: Charity Abelardo, RAC
Acting Sr. Director, Regulatory Affairs
1330 Redwood Way
Petaluma, CA 94954

Dear Ms. Abelardo:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (efinaconazole) Topical Solution, 10%.

Our (Executive) Carcinogenicity Assessment Committee ([E]CAC) reviewed your study report on November 27, 2012. As requested in your July 26, 2012 submission, a copy of the final report of the (E)CAC regarding (efinaconazole) Topical Solution, 10% is enclosed.

The recommendations made by the (E)CAC are advisory in nature and should not be interpreted as a measure of the approvability of any application for this product.

If you have any questions, call Strother D. Dixon, Regulatory Project Manager, at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

Barbara Hill, Ph.D.
Pharmacology Supervisor
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Executive CAC
Date of Meeting: November 27, 2012

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Lynnda Reid, Ph.D., DRUP, Alternate Member
Barbara Hill, Ph.D., DDDP, Supervisor
Linda Pellicore, Ph.D., DDDP, Presenting Reviewer

Author of Draft: Linda Pellicore, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA #: 203567
Drug Name: Efinaconazole Topical Solution, 10%
Sponsor: Dow Pharmaceutical Sciences

Background:

Efinaconazole Topical Solution, 10% is a triazole antifungal agent being developed for the topical treatment of onychomycosis in adults 18 years of age and older. Dose selection for the dermal mouse carcinogenicity study was based on a 13-week dose range finding study. However, the 13-week dose range finding study was not conducted with the to-be-marketed formulation. Therefore, the Executive CAC recommended that another dose range finding study be conducted with the to-be-marketed formulation to support dose selection for the dermal mouse carcinogenicity study. However, the sponsor decided to conduct the dermal mouse carcinogenicity study with the to-be-marketed formulation without conducting another dose range finding study.

Dermal Mouse Carcinogenicity Study

CD-1 mice (60 mice/sex/group) were treated with 0% (untreated control), 0% (vehicle control), 3%, 10%, or 30% efinaconazole solution. The initial dose volume was 100 µL of test article applied to an unoccluded treatment site (2 x 3cm^2). Test article was to be applied once daily, 7 days per week for up to 104 weeks. The clinical vehicle contained cyclomethicone, NF (b) (4), diisopropyl adipate (b) (4), C12-C15 alkyl lactate, (b) (4), purified water (b) (4) butylated hydroxytoluene, NF (b) (4) citric acid, USP (b) (4)), edetate disodium (b) (4) alcohol, USP (b) (4)

Severe irritation was noted at the treatment site beginning at week 20 in vehicle, low-, mid- and high-dose groups. The irritation noted at the treatment site appeared to be related to the vehicle and did increase in severity in the high-dose group. All animals were placed on a dosing holiday from week 25 to week 31 due to skin irritation and scabbing in all treatment groups. At week 31, the dose volume was decreased from 100 µL to 50 µL and the high dose group was terminated at week 34 due to severe skin effects. These modifications in the study received Executive CAC concurrence. It appeared that adequate numbers of mid- and low-dose animals survived to the end of the study.

Executive CAC Recommendations and Conclusions:

Dermal Mouse:

- The Committee concluded that the study was suboptimal due to the mice being very sensitive to severe dermal effects elicited by the vehicle. However, the Committee did not recommend repeating the dermal mouse carcinogenicity study. The Executive CAC noted the results of the chronic dermal mini-pig study conducted with once daily application of up to 30% efinaconazole solution for 9 months. No preneoplastic lesions were observed in that study and the high-dose of 30% efinaconazole was the no-observed-adverse-effect level (NOAEL) for dermal and systemic toxicity in the mini-pig.

- The Committee concurred that there were no drug-related neoplasms in the dermal mouse carcinogenicity study.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\
/Division File, DDDP
/B. Hill, Pharm/Tox Supervisor, DDDP
/L. Pellicore, Pharm/Tox reviewer, DDDP
/S. Dixon, Project Manager, DDDP
/ASeifried, OND IO

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ADELE S SEIFRIED
11/30/2012

DAVID JACOBSON KRAM
11/30/2012

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BARBARA A HILL
12/14/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203567

INFORMATION REQUEST

Dow Pharmaceutical Sciences
Attention: Charity Abelardo
Action Senior Director Regulatory Affairs
1330 Redwood Way
Petaluma, CA 94954

Dear Ms. Abelardo:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for [redacted] (b) (4) (efinaconazole) Solution, 10%.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Regarding drug substance:

- The proposed specification for drug substance is not adequate. The test method stated as [redacted] (b) (4) is not acceptable. The specification should be updated per ICH Q6A.

Regarding drug product:

- Provide more information on the novel excipient C12-15 alkyl lactate, [redacted] (b) (4)

- Specify hold-time for the bulk drug product and submit supporting data to justify. Add the bulk hold-time information to Master Batch Record. Also submit more detailed description of filling operation and its controls, and revise the filling module of the Master Batch Record accordingly.

- The acceptance criterion for total impurities of [redacted] (b) (4) is too high and it is not supported by release and stability data. Revise the acceptance criterion of the total impurities with proper justification.

- Batch analysis results indicate that an unidentified impurity with RRT [redacted] (b) (4) was observed at release of batches DP1453F1 and DP1474F1, with the concentration up to

(b) (4) However, this impurity is not shown in stability results for corresponding batches. Please explain.

Regarding method validation package

- The method validation package submitted in your application is not adequate. Please submit standalone document per 21 CFR 314.50 (e)(ii)(2)(i) with analytical procedures and related descriptive information described in the chemistry, manufacturing, and controls section for the drug substance and the drug product.

Regarding container leakage

- We are still evaluating the information provided in the NDA regarding this issue. Further communication may be forthcoming if warranted.

If you have any questions, call Cathy Tran-Zwanetz, Regulatory Project Manager, at (301) 796-3877.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Branch Chief, Branch IV
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DONNA F CHRISTNER
11/20/2012
signing as proxy for Dr. Moo-Jhong Rhee

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Division of Dermatology and Dental Product
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring MD 20993

Tel: 301 796-2110
Fax: 301 796-9894

MEMORANDUM OF TCON

Date of Teleconference: October 4, 2012
Time: 1:00 PM
Application: NDA 203567
Product: (efinaconazole) Topical Solution, 10%
Sponsor/Applicant: Dow Pharmaceutical Sciences

FDA Participants:
Julie Beitz, M.D., Director, ODE III
Stanka Kukich, M.D., Deputy Director, DDDP
David Kettl, M.D., Clinical Team Leader, DDDP
Gary Chiang, M.D., M.P.H., Clinical Reviewer, DDDP
Moo-Jhong Rhee, Ph.D., Branch Chief, Branch IV
Shulin Ding, Ph.D., Pharmaceutical Assessment Lead, DNDQA II
Bogdan Kurtyka, Ph.D., Product Quality Reviewer, DNDQA II, Branch IV
Chinmay Shukla, Ph.D., Clinical Pharmacology Reviewer, DCP 3
Barbara Gould, M.B.A.H.C.M., Chief, Project Management Staff, DDDP
Strother D. Dixon, Regulatory Health Project Manager, DDDP

Sponsor/Applicant Participants:
Charity Abelardo, Acting Senior Director, Regulatory Affairs
Varsha Bhatt, Scientist II, Team Leader, Formulation and Process Development
Sean Humphrey, Senior Specialist, Regulatory Affairs
William Jo, Nonclinical Affairs
David Lust, Senior Director Regulatory CMC
RK Pillai, Head of Dermatology Development
Pramod Sarpotdar, Executive Director, Formulation and Process Development
Kathleen Smith, Assistant Director, Clinical Operations
Simon Yeh, Director, Analytical Sciences

Purpose:
The purpose of the teleconference was to discuss the CMC potential review issues stated in the filing communication dated September 27, 2012 for pending NDA 203567 (efinaconazole) Topical Solution, 10%.

Discussion Summary:

The sponsor agreed to provide responses to filing communication comments 7-9 and labeling requests by October 24, 2012. The following comments from the filing communication were discussed and timelines were agreed upon as stated below:

2. Provide test results of USP<661> and extractables/leachables study results for the components of the brush-cap assembly, or reference to a DMF with a letter of authorization if the information resides in the DMF.

   Meeting Discussion:
   The sponsor agreed to provide the requested study results by October 24, 2012.

3. Provide quantitative results for leachables present in the registration stability samples. Alternatively, you can provide acceptable justification to support the omission of such an investigation.

   Meeting Discussion:
   The sponsor agreed to provide the requested results and/or justification by December 7, 2012.

4. Provide study results to demonstrate the compatibility of the brush with the proposed formulation. The study should include an evaluation of potential drug uptake, degradants, leachables, and brush integrity.

   Meeting Discussion:
   The sponsor stated they planned to soak the brush filaments for four weeks in 6 mL of the formulation in a tightly sealed glass container at room temperature. After which, they would measure the API and degradants by HPLC, leachables by GC-mass, and brush integrity by visual examination. The Agency recommended microscopic examination of the brushes and the sponsor agreed. The Agency also suggested that if desirable, the sponsor may shorten the duration of the study by adding additional brushes and increasing the temperature. The sponsor stated that there was a study performed with the brushes in ethanol at 50° C for 1 day.

   The sponsor agreed to provide the requested results by December 7, 2012.

5. Provide in-use stability data for the proposed product. The in-use stability study should mimic the actual use described in the package insert, and should evaluate all critical product attributes including weight loss due to evaporation and package integrity (brush, cap, bottle, label, etc.). To accurately calculate the weight loss due to evaporation, we recommend that you collect data for the weight loss due to dosing. The study duration should be at least 4 weeks. We also highly recommend that the assays of efinaconazole/related substances (b) (4), and evaluation of leachables be performed on the formulation discharged from the brush.

   Meeting Discussion:

The sponsor stated that it would be a 4-week study, and would monitor weight loss and examine package integrity (both interior and exterior surface of the bottle). The assay would be done on the discharged formulation from the brush at the initial and 4 week time points. Leachables would also be monitored.

The sponsor agreed to provide the requested data by December 7, 2012.

6. Your conclusion made in the leachables investigation report (Report No. 1206176 GC-MS Comparison of Aged and Unaged Drug Product Vehicles) is not supported by the data presented in the report. (b) (4) You should also provide GC chromatograms for individual formulation ingredients.

Meeting Discussion:
The sponsor stated that they would re-issue the report (b) (4)

The sponsor agreed to provide the requested information by December 7, 2012.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STROTHER D DIXON
11/14/2012

DAVID L KETTL
11/14/2012

STANKA KUKICH
11/15/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 203567

PROPRIETARY NAME REQUEST
UNACCEPTABLE

Dow Pharmaceutical Sciences
1330 Redwood Way
Petaluma, CA 94954-7121

ATTENTION: Charity Abelardo, RAC
Acting Sr. Director, Regulatory Affairs

Dear Ms. Abelardo:

Please refer to your New Drug Application (NDA) dated July 25, 2012, received July 26, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Efinaconazole Topical Solution, 10%.

We also refer to your August 20, 2012, correspondence, received August 20, 2012, requesting review of your proposed proprietary name, (b) (4) We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

1. (b) (4)

2 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

We note that you have proposed an alternate proprietary name in your submission dated August 20, 2012. In order to initiate the review of the alternate proprietary name, (b) (4) submit a new complete request for proprietary name review. The review of this alternate name will not be initiated until the new submission is received.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Janet Anderson, PharmD, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0675. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Strother Dixon at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CAROL A HOLQUIST
11/09/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203567

METHODS VALIDATION
MATERIALS RECEIVED

Dow Pharmaceutical Science
Attention: Charity Abelardo
Acting Sr. Director Regulatory Affairs
1330 Redwood Way
Petaluma, CA 94954

Dear Charity Abelardo:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for (b) (4) (efinaconazole) topical solution, 10% and to our September 28, 2012, letter requesting sample materials for methods validation testing.

We acknowledge receipt on October 17, 2012, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy
MVP Coordinator
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MICHAEL L TREHY
10/17/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203567

REQUEST FOR METHODS VALIDATION MATERIALS

Dow Pharmaceutical Science
Attention: Charity Abelardo
Acting Sr. Director Regulatory Affairs
1330 Redwood Way
Petaluma, CA 94954

Dear Charity Abelardo:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for [(b) (4)] (efinaconazole) topical solution, 10%.

We will be performing methods validation studies on [(b) (4)] (efinaconazole) topical solution, 10%, as described in NDA 203567.

In order to perform the necessary testing, we request the following sample materials and equipments:

Method, current version

STM 04-361 Determination of IDP-108 impurities in IDP-108 drug substance by reversed-phase HPLC
STM 04-360 Determination of IDP-108 content in IDP-108 drug substance by reversed-phase HPLC
STM-04-290 Quantitation of IDP-108, [(b) (4)] degradation products in IDP-108 formulations by RP-HPLC with UV detection

Samples and Reference Standards

10 samples of formulated product [(b) (4)] (efinaconazole) topical solution 10%
10 mL of topical solution without API for use as matrix blank
300 mg of IDP-108 drug product
300 mg of IDP-108 reference standard
1 g [(b) (4)] reference material
30 mg IDP-108 impurity [(b) (4)]
0.25 mL of IDP-108 impurity [(b) (4)]
20 mg IDP-108 impurity [(b) (4)]
20 mg IDP-108 impurity [(b) (4)]

Equipment

1	(b) (4)
1	
1	
30	

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: Michael L. Trehy
1114 Market Street, Room 1002
St. Louis, MO 63101

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy
MVP coordinator
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MICHAEL L TREHY
09/28/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203567

FILING COMMUNICATION

Dow Pharmaceutical Sciences
Attention: Charity Abelardo, RAC
Acting Sr. Director, Regulatory Affairs
1330 Redwood Way
Petaluma, CA 94954

Dear Ms. Abelardo:

Please refer to your New Drug Application (NDA) dated July 25, 2012, received July 26, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for (efinaconazole) Topical Solution, 10%.

We also refer to your amendment dated August 6, 2012.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is May 26, 2013.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by April 12, 2013.

During our filing review of your application, we identified the following potential review issues:

1. The strength, purity and quality of the drug product can not be assured due to inadequate information provided to qualify the proposed brush-cap assembly.

2. The purity of the proposed drug product can not be assured due to inadequate information provided to demonstrate the absence of significant contaminants in the formulation due to leachables from the proposed container/closure system.

3. Provide a rationale as to why it is acceptable to extrapolate the foreign clinical data to the general US population for the treatment of mild to moderate toenail onychomycosis.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

1. We acknowledge the receipt of three drug product samples, and would like to request six more representative drug product samples packaged in the to-be-marketed container/closure system for packaging evaluation.

2. Provide test results of USP<661> and extractables/leachables study results for the components of the brush-cap assembly, or reference to a DMF with a letter of authorization if the information resides in the DMF.

3. Provide quantitative results for leachables present in the registration stability samples. Alternatively, you can provide acceptable justification to support the omission of such an investigation.

4. Provide study results to demonstrate the compatibility of the brush with the proposed formulation. The study should include an evaluation of potential drug uptake, degradants, leachables, and brush integrity.

5. Provide in-use stability data for the proposed product. The in-use stability study should mimic the actual use described in the package insert, and should evaluate all critical product attributes including weight loss due to evaporation and package integrity (brush, cap, bottle, label, etc.). To accurately calculate the weight loss due to evaporation, we recommend that you collect data for the weight loss due to dosing. The study duration should be at least 4 weeks. We also highly recommend that the assays of efinaconazole/related substances (b) (4) and evaluation of leachables be performed on the formulation discharged from the brush.

6. Your conclusion made in the leachables investigation report (Report No. 1206176 GC-MS Comparison of Aged and Unaged Drug Product Vehicles) is not supported by the data presented in the report. (b) (4)

[redacted] (b) (4) You should also provide GC chromatograms for individual formulation ingredients.

7. For trial DPSI-IDP-108-P1-03, we notice that the long term storage stability data provided by you appears to be inadequate. Provide long term storage stability data for the parent compound and metabolites to support the storage stability of PK samples to cover the duration from the time of PK sample collection during the trial to the time of sample analysis. In addition, clarify the duration of storage for the internal standard solution used during analysis of samples from this trial and whether there is sufficient stability data to support such duration.

8. For trial DPSI-IDP-108-P1-02, under Section 5.3.3.1.1, Study DCN-1002550 - Bioanalytical Report, it states that the *"Stock stability has been established and is reported separately."* Provide this report for review.

9. Submit bioanalytical method validation report and bioanalysis reports for trials KP-103-02 and KP-103-03.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. Replace the "(6)" reference with the subsection for Adverse Reactions "(6.1)".

2. Bold the Highlights Limitation Statement.

3. Bold the product title.

4. Bold the "Initial U.S. Approval" statement and the date.

5. Clarify why Dow Pharmaceutical Sciences is listed on the 356h and Valeant Pharmaceuticals North America is listed on the label.

6. The FDA-Approved Patient Labeling must not be a subsection of 17.
   a. Remove 17.2 from the Patient Labeling section;
   b. In section 17, remove "(17.2)" and replace with "(Patient Information)";
   c. Remove the 17.2 subsection from the Table of Contents.

7. In the Mechanism of Action subsection, italicize "(See Microbiology 12.4)".

8. Add the word "observed" to the Adverse Reactions subsection. The following verbatim statement below should precede the presentation of adverse reactions:

   "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials or a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

We request that you resubmit labeling that addresses these issues by October 24, 2012. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information by October 24, 2012. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult Division of Dermatology and Dental Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

We acknowledge receipt of your request [redacted] (b) (4) for this application. Once we have reviewed your request, we will notify you [redacted] (b) (4) .

If you have any questions, call Strother D. Dixon, Regulatory Project Manager, at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STANKA KUKICH
09/27/2012
Signing for Julie Beitz, M.D., Director, Office of Drug Evaluation III

From:	Abelardo, Charity
To:	Jennings, Kerri-Ann
Cc:	Sosa, Aurora; David, Jeannie C
Subject:	Re: NDA 203567 (b) (4) (efinaconazole) Solution 10%
Date:	Tuesday, August 07, 2012 10:38:36 AM

Thanks Kerry. I received your voicemail yesterday after 6pm ET. I was planning to call you this morning. I will provide a response to the questions below as soon as possible today.

Kind regards,
Charity

On Aug 7, 2012, at 6:49 AM, "Jennings, Kerri-Ann" <Kerri-Ann.Jennings@fda.hhs.gov> wrote:

> Good morning Charity,
>
> Being that Sean is out of the office, I am forwarding the email below. Please follow-up as soon as possible.
>
> Thank you.
>
> Regards,
>
> Kerri-Ann
>
> _____
> **From:** Jennings, Kerri-Ann
> **Sent:** Tuesday, August 07, 2012 9:38 AM
> **To:** Humphrey, Sean (SHumphrey@dowpharmsci.com)
> **Cc:** 'charity.abelardo@dowpharmsci.com'; David, Jeannie C
> **Subject:** NDA 203567 (b) (4) (efinaconazole) Solution 10%
>
> Good morning Sean,
>
> In reference to your submission dated, July 25, 2012, please clarify the responsibilities of the following sites:
>
> Drug Substance-
>
> - Kaken Pharmaceutical Co., Ltd- Does this site perform any manufacturing or testing of the drug substance? If so, please specify.
> - Dow Pharmaceutical Sciences (DPS)- Does this site perform any manufacturing or testing of the drug substance? If so, please specify.
> - (b) (4) Does this site perform any manufacturing or testing of the drug substance? If so, please specify.
>
> In addition, submit an amendment to clarify the above.

Your prompt response is appreciated.

Please confirm receipt of this email.

Thank you.

Regards,

Kerri-Ann E. Jennings, MS, BSN, RN
LT, United States Public Health Service
Regulatory Health Project Manager
FDA/CDER/OPS/ONDQA
Division of New Drug Quality Assessment II
Phone (301) 796-2919

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KERRI-ANN JENNINGS
08/10/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203567

INFORMATION REQUEST

Dow Pharmaceutical Sciences
Attention: Charity Abelardo, RAC
Acting Sr. Director, Regulatory Affairs
1330 Redwood Way
Petaluma, CA 94954

Dear Ms. Abelardo:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (efinaconazole) Topical Solution, 10%.

We also refer to your July 25, 2012 submission, containing a New Drug Application (NDA) for (b) (4) (efinaconazole) Solution 10% for the once daily topical treatment of onychomycosis (tinea unguium).

We are reviewing the nonclinical section of your submission and have the following information request. We request a prompt written response in order to continue our evaluation of your NDA.

- Submit the SAS dataset for the dermal mouse carcinogenicity study.

If you have any questions, call Strother Dixon, Regulatory Project Manager, at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

Barbara Hill, Ph.D.
Pharmacology/Toxicology Supervisor
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Office of Biostatistics Information Sheet for Submission of Data and for Methods of Data Analysis of Carcinogenicity Studies

(The electronic data format is for two-year studies as well as transgenic mouse studies using all except the TgAC mouse models)

Revised 02/05/2008

The statistical reviewer responsible for the review of the carcinogenicity studies of this NDA/IND submission requests that the sponsor recreate the tumor data in conformance to the electronic format specified in the Agency's April 2006 guidance document entitled "*Guidance for Industry: Providing Regulatory Submissions in Electronic Format--Human Pharmaceutical Applications and Related Submissions Using the eCTD Specifications*". The guidance document can be found at http://www.fda.gov/cder/regulatory/ersr/ectd.htm under the title of the above guidance document. The cover page of the document is attached to this information sheet (Attachment A).

In Section III.D.3 of the above document the Agency gives a general description of the data formats for the pharmacology and toxicology datasets and refers readers to the associated document "*Study Data Specifications*" for more information about the format specifications of the data submission. This associated document can also be found at the above FDA website under the title of this document (or directly at http://www.fda.gov/cder/regulatory/ersr/Studydata.pdf). At this time, we are only requesting the tumor dataset in the format described on page 7 (APPENDIX 1) of the associated document. The table containing the format for tumor data in the document is attached to this information sheet (Attachment B).

Please contact the Agency to provide a time line regarding providing the tumor data. The sponsor needs to carefully meet the data format specifications in order to comply with the above guidance. Any data without 100% conformity will have to be returned for resubmission.

Note that the current draft guidance for the statistical analysis of chronic rodent carcinogenicity studies is available on the FDA web site at http://www.fda.gov/cder/guidance/815dft.pdf. Sponsors are urged to use the statistical methods recommended in the guidance to analyze the carcinogenicity study data in their IND or NDA submissions. The cover page of the document is also attached to this information sheet (Attachment C).

For questions related to the data format and the methods of statistical analysis, please contact Karl K. Lin, Ph.D., Room 5238, Building 22, Office of Biostatistics, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, 301-796-0943, karl.lin@fda.hhs.gov.

(Attachment A)

Cover page of "*Guidance for Industry: Providing Regulatory Submissions in Electronic Format--Human Pharmaceutical Applications and Related Submissions Using the eCTD Specifications*"

Guidance for Industry

Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

April 2006
Electronic Submissions

Revision 1

(Attachment B)

Data format table on page 7 (APPENDIX 1) of the associated document "*Study Data Specifications*"

Tumor Dataset For Statistical Analysis[1,2] (tumor.xpt)				
Variable	**Label**	**Type**	**Codes**	**Comments**
STUDYNUM	Study number	char		[3]
ANIMLNUM	Animal number	char		[1,3]
SPECIES	Animal species	char	M=mouse R=rat	
SEX	Sex	char	M=male F=female	
DOSEGP	Dose group	num	Use 0, 1, 2, 3,4,... in ascending order from control. Provide the dosing for each group.	
DTHSACTM	Time in days to death or sacrifice	num		
DTHSACST	Death or sacrifice status	num	1 = Natural death or moribund sacrifice 2 = Terminal sacrifice 3 = Planned intermittent sacrifice 4= Accidental death	
ANIMLEXM	Animal microscopic examination code	num	0= No tissues were examined 1 = At least one tissue was examined	
TUMORCOD	Tumor type code	char		[3,4]
TUMORNAM	Tumor name	char		[3,4]
ORGANCOD	Organ/tissue code	char		[3,5]
ORGANNAM	Organ/tissue name	char		[3,5]
DETECTTM	Time in days of detection of tumor	num		
MALIGNST	Malignancy status	num	1 = Malignant 2= Benign 3 = Undetermined	[4]
DEATHCAU	Cause of death	num	1 = Tumor caused death 2= Tumor did not cause death 3 = Undetermined	[4]
ORGANEXM	Organ/Tissue microscopic examination code	num	1 = Organ/Tissue was examined and was usable 2= Organ/Tissue was examined but was not usable (e.g., autolyzed tissue) 3 = Organ/Tissue was not examined	

[1] Each animal in the study should have at least one record even if it does not have a tumor.

[2] Additional variables, as appropriate, can be added to the bottom of this dataset.

[3] ANIMLNUM is limited to no more than 12 characters; ORGANCOD and TUMORCOD are limited to no more than 8 characters; ORGANNAM and TUMORNAM should be as concise as possible.

[4] A missing value should be given for the variable MALIGNST, DEATHCAU, TUMORNAM and TUMORCOD when the organ is unuseable or not examined.

[5] Do not include a record for an organ that was useable and no tumor was found on examination. A record should be included for organs with a tumor, organs found unusable, and organs not examined.

(Attachment C)

Cover page of *"Guidance for Industry: Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals"*

Guidance for Industry

Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857. All comments should be identified with the docket number listed in the notice of availability.

For questions regarding this draft document contact (CDER) Karl K. Lin, Ph.D., 301-796-0943, e-mail link.lin@fda.hhs.gov or link@cder.fda.gov

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

May 2001

Pharm/Tox

C:\Data\My Documents #1 A-M\Guidance04232001NncyDerr.DOC
11/22/05

Guidance for Industry

Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857. All comments should be identified with the docket number listed in the notice of availability.

For questions regarding this draft document contact (CDER) Karl K. Lin, Ph.D., 301-827-3093, e-mail link @cder fda.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

May 2001

Pharm/Tox

G \815dft.doc
04/23/01

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BARBARA A HILL
08/02/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 77732

MEETING MINUTES

Dow Pharmaceutical Sciences (DPS)
Attention: Charity Abelardo, RAC
Acting Senior Director, Regulatory Affairs
1330 Redwood Way
Petaluma, CA 94954-7121

Dear Ms. Abelardo:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for IDP-108 (efinaconazole) Solution, 10%.

We also refer to the meeting scheduled on April 17, 2012 between representatives of your firm and the FDA. The purpose of the meeting was to gain agreement that the information contained in the technical data sections are adequate for a 505(b)(1) NDA filing and to gain feedback for questions related to content/format of the NDA. Your premeeting briefing package (submitted February 22, 2012) provides background and questions for discussion.

We acknowledge email with Barbara Gould on April 15, 2012, notifying us that after receipt and review of the premeeting communication consisting of Agency responses to your questions, you have determined that the responses to your questions are sufficient and additional discussion is not necessary.

This letter and the enclosed final responses represent the official record.

If you have any questions, call Barbara Gould, Chief, Project Staff Management, at (301) 796-4224.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, M.D., F.A.A.D.
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure – Final Responses

FINAL RESPONSES

IND 077732

Product: (efinaconazole) Solution, 10%

Regulatory Path: 505(b)(1)

Sponsor: Dow Pharmaceutical Sciences

Proposed Indication: Topical treatment of [redacted] (b) (4) onychomycosis in patients 18 years or older

Type of Meeting: Type B

Meeting Date: April 18, 2012

Introductory Comment:

This material includes the Agency's final responses to the questions submitted for your meeting scheduled for April 18, 2012, at 10:00 am in White Oak Building 22 between Dow Pharmaceutical Sciences and the Division of Dermatology and Dental Products. This material was shared to promote a collaborative and successful discussion at the meeting. After receipt of the preliminary responses, you had two options:

- If these answers and comments were clear to you and you determined that further discussions were not required, you had the option of canceling the meeting.

- If you determined that discussion was needed for only some of the original questions, you had the option of reducing the agenda and/or changing the format of the meeting (e.g., from face-to-face to telecon).

You conveyed to Barbara Gould via email on April 15, 2012 that the responses to your questions were sufficient and additional discussion was not necessary. However, you requested clarification with regard to the responses provided under Question 2 and the additional information requested by FDA for inclusion in the NDA submission. As such, the below responses represent our final responses to your questions.

Purpose of the Meeting:
To gain agreement that the information contained in the technical data sections are adequate for a 505(b)(1) NDA filing and to gain feedback for questions related to content/format of the NDA.

Regulatory Correspondence History

We have had the following meetings with you:

- 8/17/2009 – End of Phase 2 Meeting

We have sent the following correspondences:

- 11/24/2009 – Advice
- 4/14/2010 – Advice/Information Request
- 4/14/2010 – Advice/Information Request
- 4/14/2010 – Advice/Information Request
- 8/30/2010 – Advice
- 2/14/2011 – Advice/Information Request
- 2/25/2011 – Advice
- 3/16/2011 – Advice
- 4/18/2011 – Advice

Regulatory

Question [1]:

Does the Agency agree that efinaconazole solution meets the regulatory standards for priority review?

Response:

No, the Agency does not agree that efinaconazole solution for the treatment of onychomycosis qualifies for priority review. You have not provided an adequate rationale that your proposed product provides for a significant improvement over existing therapies for a non-life threatening disease.

In order to qualify for priority review, you will need to provide an adequate rationale that your proposed product has the potential to provide significant advances in the treatment of onychomycosis. There are several currently approved therapies for onychomycosis. The preliminary efficacy analysis for your proposed product claims to show a primary efficacy response rate of about 16%, which is similar to at least one currently approved therapy. Approximately 84% of subjects would fail to respond to your proposed treatment.

Chemistry, Manufacturing and Controls (CMC)

No CMC questions were submitted in the briefing package for this meeting. After reviewing the limited CMC information provided in the briefing package, we have the following comments:

1. The proposed drug substance specification should include tests on chiral purity and residual solvents with appropriate acceptance criteria.

2. Address the issues of [redacted] (b) (4) carried over from excipients for drug product in the proposed NDA.

3. To support the proposed container/closure system for the drug product, provide test results of USP<661> for each formulation-contacting packaging component. Additionally, due to the high level (b) (4) in the proposed formulation, provide the results of the extractables study (b) (4) and your investigation on leachables in the registration stability studies.

Pharmacology/Toxicology

Question [1]:
Does the Agency agree that the completed nonclinical program, as detailed in Section 8, is sufficient to characterize efinaconaozle toxicity for the NDA and that no other studies are required?

Response:
Yes.

Question [2]:
Does the Agency agree that the toxicity evaluation of the impurities have been fully addressed and no further studies will be required?

Response:
Yes.

Question [3] (microbiology question [1]):
Does the Agency agree with the proposed format and location for the specified studies and respective CTD sections described above?

Response:
Yes, the Agency agrees with the proposed format and location of clinical microbiology summaries and study reports.

Clinical

Question [1]:
Does the Agency agree to waive phototoxicity and photoallergy studies?

Response:
Yes, a waiver is likely to be appropriate at the time of NDA review. The submitted spectra for IDP-108A solutions, 5% and 10% w/w, and the IDP-108 (b) (4) solutions, 1% and 10%, and their excipients do not demonstrate any absorbance in the wavelength range of 290 to 700nm.

Question [2]:
Based on the completion of the clinical program as detailed in Section 9, does the agency agree that the clinical program is adequate to support approval of efinaconazole solution

with an indication for the topical treatment of (b) (4) onychomycosis in patients 18 years or older?

Response:
The clinical program presented in Section 9 appears to be adequate to meet NDA filing requirements; however, the adequacy of data and NDA approval will be the subject of the Agency NDA review.

Question [3]:
Does the Agency agree that the total patient exposure is adequate to support approval of the NDA?

Response:
It does appear that sufficient exposure to efinaconazole solution has been established to satisfy the ICH E1A guidelines. The adequacy of the safety data will be reviewed during the NDA review process, and supplementary safety information may be requested should additional safety issues be identified.

Question [4]:
Does the Agency agree that (b) (4) based upon the conditions described?

Response:
A (b) (4)

Biostatistics

Question [1]:
The complete list of efinaconazole clinical studies (IND and non-IND) is presented in Table 17. The datasets for the following clinical trials will be included in the NDA in CDISC format:

- DPSI-IDP-108-P3-01 (Phase 3 safety and efficacy)
- DPSI-IDP-108-P3-02 (Phase 3 safety and efficacy)
- DPSI-IDP-108-P2-01 (Phase 2 safety and efficacy)
- DPSI-IDP-108-P1-03 (Phase 1 PK)

The datasets for all other IND studies (DPSI-IDP-108-P1-01 and DPSI-IDP-108-P1-02) will be included in the NDA as SAS transport files. Datasets for the remaining two clinical studies not conducted under IND 077732 will not be included.

Does the Agency agree with the provision of the files in this format?

Response:
1. The electronic datasets for clinical studies in should be submitted in SAS transport form (.xpt).

2. You should submit both SDTM datasets (raw data directly from the CRF in standardized format) and analysis datasets for the Phase 2 and 3 studies. Each analysis dataset should include the treatment assignments, baseline assessments, and key demographic variables. The analysis datasets should include all variables needed for conducting all primary, secondary, and sensitivity analyses included in the study report. For endpoints that include imputations, both observed and imputed variables should be included and clearly identified.

3. For Study DPSI-IDP-108-P1-03 (Phase 1 PK) we recommend that you provide the raw and calculated PK parameters in a SAS transport file as well.

4. Include dataset documentation (define.xml and define.pdf) for SDTM and analysis datasets. Definition files for raw datasets modeled according to CDISC/SDTM IG and standards should be submitted as .xml file types (define.xml). Refer to CDISC's Define.XML page for assistance/guidance related to creating define.xml files for CDISC/SDTM data. Also, for ease of viewing by the reviewer and printing, submit corresponding define.pdf files in addition to the define.xml. The analysis dataset documentation (define.pdf file) should include sufficient detail, such as definitions or descriptions of each variable in the data set, algorithms for derived variables (including source variables used), and descriptions for the codes used in factor variables.

5. Statistical programs for any non-standard analyses should be submitted.

6. If any subjects were enrolled in more than one study, include a unique subject ID that permits subjects to be tracked across multiple studies.

In addition to the electronic data sets, the NDA submission should include the following items for the Phase 2 and 3 studies:

   a. Study protocols including the statistical analysis plan, all protocol amendments (with dates), and an annotated copy of the Case Report Form (which maps variables in the datasets to the CRF).

   b. The generated treatment assignment lists and the actual treatment allocations (along with date of enrollment) from the trials.

Question [2]:
Datasets will be provided for the clinical studies conducted under IND 077732 and included in the eCTD NDA. Does the Agency agree that submission of data listings will not be necessary?

Response:
Yes, provided that the information is included in the electronic datasets.

Question [3]:
Statistical analysis of the safety data for the 52 week Phase 3 trials DPSI-IDP-108-P3-01 and DPSI-IDP-108-P3-02 conducted with the to-be-marketed formulation will be pooled and presented in the Integrated Summary of Safety (ISS).

Does the Agency agree with the statistical analysis plan for pooling of safety data as described above for the Phase 3 clinical studies?

Response:
Your approach appears reasonable. If you intend to pool safety data from earlier phase studies, provide justification and methods in which these pooled safety data is appropriate. In addition to the information required in the Integrated Summary of Safety to aid our review, please provide the following:

- Shift tables for all laboratory values for both outside the normal range and outside the range that is considered clinically significant. Please provide the normal range of values for all parameters, the threshold for concern for a clinically significant change and your justification for why this threshold is appropriate.

Question [4]:
Statistical analysis of the efficacy data for the 52 week Phase 3 trials DPSI-IDP-108-P3-01 and DPSI-IDP-108-P3-02 conducted with the to-be-marketed formulation will be pooled and presented in the Integrated Summary of Efficacy (ISE).

Does the Agency agree with the statistical analysis plan for pooling of efficacy data?

Response:
Your approach appears reasonable.

In addition to the information required in the Integrated Summary of Effectiveness to aid our review, please provide the following:

- Provide a detailed analysis for race (i.e., beyond white vs. non-white)
- Provide a detailed analysis for age subgroups.
- Provide a rationale for why the data presented represents a demonstration of substantial evidence of effectiveness for the proposed indication.

Refer to the *Guidance for Industry: Integrated Summary of Effectiveness* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079803.pdf) for additional information on what to include in the ISE.

The Study Data Specifications require the submission to include all datasets in the SAS Transport format (v5). Any questions regarding the Study Data Specifications can be submitted to esub@fda.hhs.gov.

Questions for Clarification:

Clarifying Question [1]:
The response to Biostatistics Question [1] (lines 157 to 169) found on lines 171 to 210 was very much appreciated. Additionally, we would like to confirm our understanding related to the following question.

The two clinical studies not conducted under IND 077732 (KP-103-02 and KP-103-02 extracted from Table 17 below) were conducted by our development partner Kaken Pharmaceutical Co., LTD. The demonstration of safety and efficacy does not depend on the results of these studies. The full clinical study reports are being submitted in the NDA only as ancillary information obtained during the clinical development program. Both non-IND studies will be summarized in the Integrated Summary of Safety. On lines 166 to 167 we indicated that the datasets for these studies would not be included in the NDA.

Does the Agency agree that these datasets do not need to be included in the NDA?

Extract from Pre-NDA Meeting Briefing Document [Table 17, page 49]

Type of Study/ (Study Identifier)	**Location of Study Report/Type of Report**	**Objective(s) of the Study**	**Study Design and Type of Control/Treatment Duration**	**Test Products; Dosage Regimen; Route of Administration**	**No.of Subjects**	**Healthy Subjects or Diagnosis of Patients**
Phase 1 Investigation of efinaconazole concentration in nails (Non-IND Study) KP-103-03	Section 5.3.4.2/Full	To investigate efinaconazole concentrations in the effected vs normal toenails as well as the first vs second toenail with different nail thickness	Open label study with repeated application of efinaconazole to all toenails./28 days	5% and 10% efinaconazole applied topically once daily	40	Diseased
Phase 1 Skin irritation and photosensitization (Non-IND Study) KP-103-02	Section 5.3.5.1/Full	Evaluation of Skin irritation and photosensitization of efinaconazole	Positive control and negative controlled Patch test and photo patch test using Latin square method skin irritation and photosensitization of single application in step 1. Skin irritation of repeated application for 7 days./7 days	Placebo, 0.2% sodium lauryl sulfate, deionized water, 1%, 5% and 10% Solution applied topically once daily	56	Healthy adult males

Response:
Your proposal is acceptable provided the waiver for phototesting is granted during the NDA review. The Agency may have additional information requests related to these study reports if safety issues become apparent during the NDA review process.

Extract from Pre-NDA Meeting Briefing Document [Table 17, page 49]

Type of Study/ (Study Identifier)	Location of Study Report/Type of Report	Objective(s) of the Study	Study Design and Type of Control/Treatment Duration	Test Products; Dosage Regimen; Route of Administration	No.of Subjects	Healthy Subjects or Diagnosis of Patients
Phase 1 Investigation of efinaconazole concentration in nails (Non-IND Study) KP-103-03	Section 5.3.4.2/Full	To investigate efinaconazole concentrations in the effected vs normal toenails as well as the first vs second toenail with different nail thickness	Open label study with repeated application of efinaconazole to all toenails./28 days	5% and 10% efinaconazole applied topically once daily	40	Diseased
Phase 1 Skin irritation and photosensitization (Non-IND Study) KP-103-02	Section 5.3.5.1/Full	Evaluation of Skin irritation and photosensitization of efinaconazole	Positive control and negative controlled Patch test and photo patch test using Latin square method skin irritation and photosensitization of single application in step 1. Skin irritation of repeated application for 7 days./7 days	Placebo, 0.2% sodium lauryl sulfate, deionized water, 1%, 5% and 10% Solution applied topically once daily	56	Healthy adult males

Clarifying Question [2]:
On lines 232 to 237 the Agency requested the following:

> *Shift tables for all laboratory values for both outside the normal range and outside the range that is considered clinically significant. Please provide the normal range of values for all parameters, the threshold for concern for a clinically significant change and your justification for why this threshold is appropriate.*

As requested, the submission will include shift tables to present all laboratory values outside the normal range and the normal range for all parameters. As specified in the study protocols, the determination of the clinical significance of an outside of normal range laboratory value was the decision of the site investigators and did not involve a pre-specified threshold value. Thus, the tables that present the out of range laboratory values do not identify those reported as clinically significant.

The tables described above will be augmented with a set that will include only those laboratory value shifts from a baseline value of "not clinically significant" to a post baseline value of "clinically significant" and visa versa.

Does the combined set of shift tables satisfy the informational request for all laboratory values which are both outside the normal range and outside the range as well as considered clinically significant?

Response:
Your proposal is acceptable.

Clarifying Question [3]:
Re: Question [2] on lines 212 to 215 reads:

> *Datasets will be provided for the clinical studies conducted under IND 077732 and included in the eCTD NDA. Does the Agency agree that submission of data listings will not be necessary?*

The Agency's response on line 218 was:

> *Yes, provided that the information is included in the electronic datasets.*

It is our understanding that for the overall evaluation of the NDA the line listings that include all sites combined are not necessary if the information is included in the electronic datasets, but site specific individual subject data ("line") listings are requested by the Office of Scientific Investigations (OSI) for the Phase 3 studies. In addition, we are requested to participate in the OSI pilot program for submission of site-level datasets intended to facilitate timely selection of clinical sites for FDA inspection and, by extension, Agency evaluation of the NDA.

The additional information requested by OSI (Item 1, 2 and 3) were not anticipated to be provided at the time of NDA submission and represent a significant volume of information not generally required as part of the original NDA in the form requested. DPS would like to propose that the information requested by OSI be provided as an Amendment to the NDA within 2 weeks following NDA filing (Day 60).

Does the Agency agree that the additional body of information requested to facilitate FDA site inspections can be provided as an Amendment to the NDA?

Response:
Your New Drug Application should be complete at the time of submission.

Clarifying Question [4]:
We would like to take this opportunity to confirm that DPS has submitted a response to the letter from the Division dated February 27, 2012, which provided advice and a

request for information regarding the Statistical Analysis Plans (SAPs) for the Phase 3 studies. The response was submitted on March 22, 2012 (S-0055).

The briefing book for the Pre-NDA meeting was submitted prior to our receipt of the Division's letter and request for information (S-0053; February 21, 2012). Consequently, our meeting briefing materials submitted in preparation for the Pre-NDA meeting did not reflect our intentions for inclusion of the analyses based on the Divisions recommendation to follow the originally approved SAPs.

Based on the Agency's recommendations, and for purposes of completeness, the two Phase 3 clinical study reports and the overall integrated summary of efficacy will include the analyses defined and described within the originally approved SAPs (SAP Version 1) that follow the original versions of the protocols, as well as the analyses defined and described in the revised SAPs that were approved prior to database lock and unblinding of the treatment assignments (SAPs Version 2).

The clinical overview and summary in the NDA will focus on the Agency's preferred secondary analysis endpoints (i.e., those based on SAP version 1) and will describe all other analyses (i.e., those based on SAP version 2) as supportive.

Does the Agency concur with our plan to implement the Division's recommendations?

Response:
Your proposal appears reasonable.

Administrative Comments

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND or NDA might identify additional comments or information requests.

2. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21 CFR 54 and 21CFR 314.50(k).

3. We remind you of the Pediatric Research Equity Act of 2007 which requires all applications for a new active ingredient, new dosage form, new indication, new route of administration, or new dosing regimen to contain an assessment of the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations unless this requirement is waived or deferred.

4. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry: Qualifying for Pediatric

Exclusivity for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

MANUFACTURING FACILITIES

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct the inspections (Item I and II).

The dataset that is requested as per Item III below, is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 2, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and specific Clinical Investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed Phase 3 clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Current Location of Principal Investigator (if no longer at Site): Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)

2. Please include the following information in a tabular format by site in the original NDA for each of the completed Phase 3 clinical trials:
   a. Number of subjects screened for each site by site
   b. Number of subjects randomized for each site by site
   c. Number of subjects treated who prematurely discontinued for each site by site

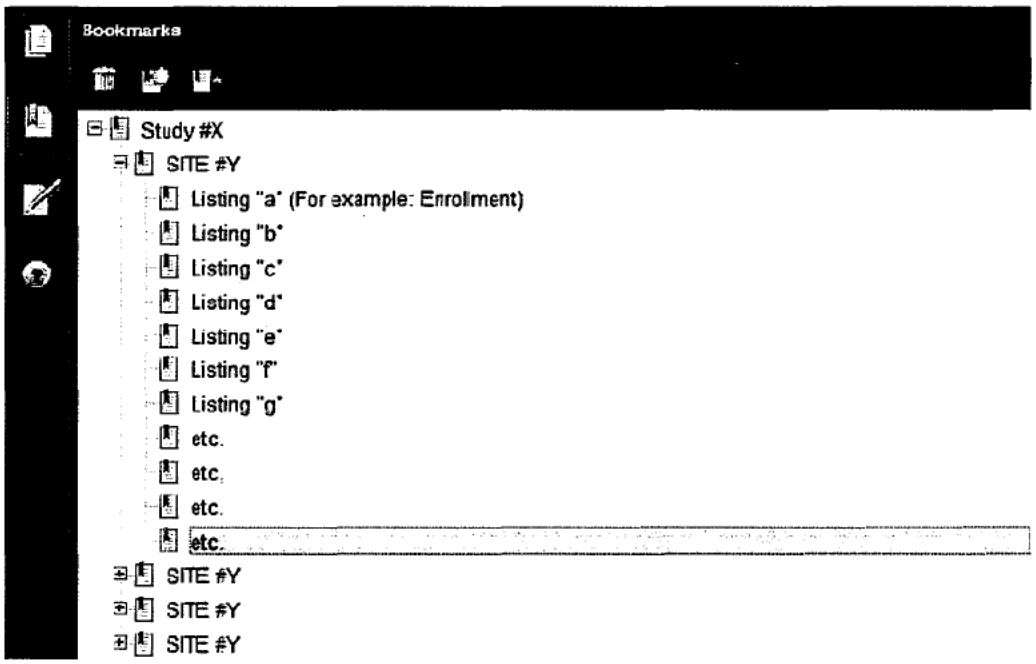
3. Please include the following information in a tabular format in the NDA for each of the completed Phase 3 clinical trials:
   a. Location of Trial Master File [actual physical site(s) where documents are maintained and would be available for inspection]
   b. Name, address and contact information of all CROs used in the conduct of the clinical trials
   c. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies
   d. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)

4. For each pivotal trial provide a sample annotated Case Report Form (if items are provided elsewhere in submission, please describe location or provide a link to requested information).
5. For each pivotal trial provide original protocol and all amendments (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data ("line") listings. For each site provide line listings for:
   a. Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements
   b. Subject listing for treatment assignment (randomization)
   c. Subject listing of drop-outs and subjects that discontinued with date and reason
   d. Evaluable subjects/ non-evaluable subjects and reason not evaluable
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of laboratory tests performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to Attachment 1, "Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions" for further information. We request that you provide a dataset, as outlined, which includes requested data for each pivotal study submitted in your application.

Attachment 1

1. Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions

1.1. INTRODUCTION

The purpose of this pilot for electronic submission of a single new clinical site dataset is to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process in support of the evaluation of data integrity.

1.2. DESCRIPTION OF THE SUMMARY LEVEL CLINICAL SITE DATASET

The summary level clinical site data are intended (1) to clearly identify individual clinical investigator sites within an application or supplement, (2) to specifically reference the studies to which those clinical sites are associated, and (3) to present the characteristics and outcomes of the study at the site level.

For each study used to support efficacy, data should be submitted by clinical site and treatment arm for the population used in the primary analysis to support efficacy. As a result, a single clinical site may contain multiple records depending on the number of studies and treatment arms supported by that clinical site.

The site-level efficacy results will be used to support site selection to facilitate the evaluation of the application. To this end, for each study used to support efficacy, the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

The following paragraphs provide additional details on the format and structure of the efficacy related data elements.

Site-Specific Efficacy Results

For each study and investigator site, the variables associated with efficacy and their variable names are:

- Treatment Efficacy Result (TRTEFFR) – the efficacy result for each primary endpoint, by treatment arm (see below for a description of endpoint types and a discussion on how to report this result)

- Treatment Efficacy Result Standard Deviation (TRTEFFS) – the standard deviation of the efficacy result (treatEffR) for each primary endpoint, by treatment arm

- Site-specific Efficacy Effect Size (SITEEFFE) – the effect size should be the same representation as reported for the primary efficacy analysis

- Site-specific Efficacy Effect Size Standard Deviation (SITEEFFS) – the standard deviation of the site-specific efficacy effect size (SITEEFFE)

- Endpoint (endpoint) – a plain text label that describes the primary endpoint as described in the Define file data dictionary included with each application.

- Treatment Arm (ARM) – a plain text label for the treatment arm that is used in the Clinical Study Report.

In addition, for studies whose primary endpoint is a time-to-event endpoint, include the following data element:

- Censored Observations (CENSOR) –the number of censored observations for the given site and treatment.

If a study does not contain a time-to-event endpoint, record this data element as a missing value.

To accommodate the variety of endpoint types that can be used in analyses please reference the below endpoint type definitions when tabulating the site-specific efficacy result variable by treatment arm, "TRTEFFR."

- Discrete Endpoints – endpoints consisting of efficacy observations that can take on a discrete number of values (e.g., binary, categorical). Summarize discrete endpoints by an event frequency (i.e., number of events), proportion of events, or similar method at the site for the given treatment.

- Continuous Endpoints – endpoints consisting of efficacy observations that can take on an infinite number of values. Summarize continuous endpoints by the mean of the observations at the site for the given treatment.

- Time-to-Event Endpoints – endpoints where the time to occurrence of an event is the primary efficacy measurement. Summarize time-to-event endpoints by two data elements: the number of events that occurred (TRTEFFR) and the number of censored observations (CENSOR).

- Other – if the primary efficacy endpoint cannot be summarized in terms of the previous guidelines, a single or multiple values with precisely defined variable interpretations should be submitted as part of the dataset.

In all cases, the endpoint description provided in the "endpoint" plain text label should be expressed clearly to interpret the value provided in the (TRTEFFR) variable.

The site efficacy effect size (SITEEFFE) should be summarized in terms of the primary efficacy analysis (e.g., difference of means, odds ratio) and should be defined identically for all records in the dataset regardless of treatment.

The Define file for the dataset is presented in Exhibit 1: *Table 1 Clinical Site Data Elements Summary Listing (DE)*. A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (*.xpt).

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
1	STUDY	Study Number	Char	String	Study or trial identification number.	ABC-123
2	STUDYTL	Study Title	Char	String	Title of the study as listed in the clinical study report (limit 200 characters)	Double blind, randomized placebo controlled clinical study on the influence of drug X on indication Y
3	DOMAIN	Domain Abbreviation	Char	String	Two-character identification for the domain most relevant to the observation. The Domain abbreviation is also used as a prefix for the variables to ensure uniqueness when datasets are merged.	DE
4	SPONNO	Sponsor Number	Num	Integer	Total number of sponsors throughout the study. If there was a change in the sponsor while the study was ongoing, enter an integer indicating the total number of sponsors. If there was no change in the sponsor while the study was ongoing, enter "1".	1
5	SPONNAME	Sponsor Name	Char	String	Full name of the sponsor organization conducting the study at the time of study completion, as defined in 21 CFR 312.3(a).	DrugCo, Inc.
6	IND	IND Number	Num	6 digit identifier	Investigational New Drug (IND) application number. If study not performed under IND, enter -1.	010010
7	UNDERIND	Under IND	Char	String	Value should equal "Y" if study at the site was conducted under an IND and "N" if study was not conducted under an IND (i.e., 21 CFR 312.120 studies).	Y
8	NDA	NDA Number	Num	6 digit identifier	FDA new drug application (NDA) number, if available/applicable. If not applicable, enter -1.	021212
9	BLA	BLA Number	Num	6 digit identifier	FDA identification number for biologics license application, if available/applicable. If not applicable, enter -1.	123456
10	SUPPNUM	Supplement Number	Num	Integer	Serial number for supplemental application, if applicable. If not applicable, enter -1.	4
11	SITEID	Site ID	Char	String	Investigator site identification number assigned by the sponsor.	50
12	ARM	Treatment Arm	Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters).	Active (e.g., 25mg), Comparator drug product name (e.g., Drug x), or Placebo
13	ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site by treatment arm.	20
14	SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site.	100
15	DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site by treatment arm as defined in the clinical study report.	5

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
16	ENDPOINT	Endpoint	Char	String	Plain text label used to describe the primary endpoint as described in the Define file included with each application (limit 200 characters).	Average increase in blood pressure
17	ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other).	Continuous
18	TRTEFFR	Treatment Efficacy Result	Num	Floating Point	Efficacy result for each primary endpoint by treatment arm at a given site.	0, 0.25, 1, 100
19	TRTEFFS	Treatment Efficacy Result Standard Deviation	Num	Floating Point	Standard deviation of the efficacy result (TRTEFFR) for each primary endpoint by treatment arm at a given site.	0.065
20	SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	Site effect size with the same representation as reported for the primary efficacy analysis.	0, 0.25, 1, 100
21	SITEEFFS	Site-Specific Efficacy Effect Size Standard Deviation	Num	Floating Point	Standard deviation of the site-specific efficacy effect size (SITEEFFE).	0.065
22	CENSOR	Censored Observations	Num	Integer	Number of censored observations at a given site by treatment arm. If not applicable, enter -1.	5
23	NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site by treatment arm. This value should include multiple events per subject and all event types (i.e., not limited to only those that are deemed related to study drug or treatment emergent events).	10
24	SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site by treatment arm. This value should include multiple events per subject.	5
25	DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site by treatment arm.	1
26	PROTVIOL	Number of Protocol Violations	Num	Integer	Number of protocol violations at a given site by treatment arm as defined in the clinical study report. This value should include multiple violations per subject and all violation type (i.e., not limited to only significant deviations).	20
27	FINLMAX	Maximum Financial Disclosure Amount	Num	Floating Point	Maximum financial disclosure amount ($USD) by any single investigator by site. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	20000.00
28	FINLDISC	Financial Disclosure Amount	Num	Floating Point	Total financial disclosure amount ($USD) by site calculated as the sum of disclosures for the principal investigator and all sub-investigators to include all required parities. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	25000.00

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
29	LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572.	Doe
30	FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572.	John
31	MINITIAL	Investigator Middle Initial	Char	String	Middle initial of the investigator, if any, as it appears on the FDA 1572.	M
32	PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
33	FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
34	EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator.	john.doe@mail.com
35	COUNTRY	Country	Char	ISO 3166-1-alpha-2	2 letter ISO 3166 country code in which the site is located.	US
36	STATE	State	Char	String	Unabbreviated state or province in which the site is located. If not applicable, enter NA.	Maryland
37	CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located.	Silver Spring
38	POSTAL	Postal Code	Char	String	Postal code in which site is located. If not applicable, enter NA.	20850
39	STREET	Street Address	Char	String	Street address and office number at which the site is located.	1 Main St, Suite 100

The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of 205 subjects who were randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy effect size (SITEEFFE) is the difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, each site contains 2 rows in the following example data set and a total of 8 rows for the entire data set.

Exhibit 2: Example for Clinical Site Data Elements Summary Listing (Table 1)

STUDY	STUDYTL	DOMAIN	SPONNO	SPONNAME	IND	UNDERIND	NDA	BLA	SUPPNUM	SITEID	ARM	ENROLL	SCREEN	DISCONT
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Active	26	61	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Placebo	25	61	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Active	23	54	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Placebo	25	54	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Active	27	62	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Placebo	26	62	5
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Active	26	60	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Placebo	27	60	1

ENDPOINT	ENDTYPE	TRTEFFR	TRTEFFS	SITEEFFE	SITEEFFS	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLMAX	FINLDISC	LASTNAME	FRSTNAME
Percent Responders	Binary	0.48	0.0096	0.34	0.0198	-1	0	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.14	0.0049	0.34	0.0198	-1	2	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.48	0.0108	0.33	0.0204	-1	3	2	1	0	45000.00	45000.00	Washington	George
Percent Responders	Binary	0.14	0.0049	0.33	0.0204	-1	0	2	0	3	20000.00	45000.00	Washington	George
Percent Responders	Binary	0.54	0.0092	0.35	0.0210	-1	2	2	0	1	15000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.19	0.0059	0.35	0.0210	-1	3	6	0	0	22000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.46	0.0095	0.34	0.0161	-1	4	1	0	0	0.00	0.00	Lincoln	Abraham
Percent Responders	Binary	0.12	0.0038	0.34	0.0161	-1	1	2	0	1	0.00	0.00	Lincoln	Abraham

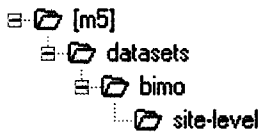
MINITIAL	PHONE	FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.

Attachment 2
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUSAN J WALKER
05/14/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203567

NDA ACKNOWLEDGMENT

Dow Pharmaceutical Sciences
Attention: Charity Abelardo, RAC
Acting Sr. Director, Regulatory Affairs
1330 Redwood Way
Petaluma, CA 94954

Dear Ms. Abelardo:

We have received your New Drug Application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: (b) (4) (efinaconazole) Topical Solution, 10%

Date of Application: July 26, 2012

Date of Receipt: July 26, 2012

Our Reference Number: NDA 203567

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on September 24, 2012, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatology and Dental Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

Strother D. Dixon
Regulatory Health Project Manager
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STROTHER D DIXON
07/27/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 77,732

MEETING MINUTES

Dow Pharmaceutical Sciences, Inc.
Attention: Barry Calvarese, MS
Vice-President, Regulatory and Clinical Affairs
1330 Redwood Way
Petaluma, California 94954

Dear Mr. Calvarese:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for IDP-108 (KP-103) Solution, 10%.

We also refer to the meeting between representatives of your firm and the FDA on August 4, 2009. The purpose of the meeting was to gain FDA's agreement on the development program to support the approval of a 505 (b)(1) NDA for IDP-108 10% Solution for the treatment of onychomycosis of the toenails (b) (4)

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Nichelle Rashid, Regulatory Project Manager at (301) 796-3904.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, M.D., F.A.A.D.
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure – Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	End of Phase 2
Meeting Date and Time:	August 4, 2009, 10:00 am
Meeting Location:	White Oak, Building 22, Conference Room 1421
Application Number:	IND 77,732
Product Name:	IDP-108 (KP-103) Solution, 10%
Indication:	Treatment of mild to moderate onychomycosis of the toenails (b) (4)
Sponsor/Applicant Name:	Dow Pharmaceutical Sciences, Inc.
Meeting Chair:	Susan Walker, M.D.
Meeting Recorder:	Nichelle Rashid

FDA ATTENDEES

Susan Walker, M.D., F.A.A.D., Director, DDDP
David Kettl, M.D., Clinical Team Leader, DDDP
Brenda Vaughan, M.D., Clinical Reviewer, DDDP
Barbara Hill, Ph.D., Pharmacology Supervisor, DDDP
Kathleen Fritsch, Ph.D., Biostatistics Reviewer, DB III
Dennis Bashaw, Pharm.D., Director, DCP III
Shulin Ding, Ph.D., Pharmaceutical Assessment Lead, DPMA II, Branch III
Margo Owens, Project Management Team Leader, DDDP
Nichelle E. Rashid, Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES

Dow Pharmaceutical Sciences, Incorporated

Barry M. Calvarese, M.S., Vice-President, Regulatory and Clinical Affairs
Diana Chen, M.D., F.A.A.D., Vice-President, Medical Affairs
Gordon Dow, Ph.D., Founder and Chief Technical Officer
AJ Acker, RAC, Senior Manager, Regulatory Affairs
Radhakrishnan Pillai, Ph.D., Associate Director, Project Management
Michelle Carpenter, JD, RAC, Executive Director, Regulatory Affairs
Charles Chavdarian, Ph.D, Executive Director, Analytical Sciences and Regulatory CMC
Pramod Sarpotdar, Ph.D., Senior Director, Formulation Sciences
Larry Amdahl, B.S., Director, Clinical Affairs

Roberto Cortes, M.D., Director, Drug Safety
Linda Mutter, Ph.D., Director, Nonclinical
Kathleen Smith, MDA, Senior Manager, Clinical Affairs
Marian Glynn, Toxicologist, Nonclinical Regulatory Affairs

(b) (4)

1.0 BACKGROUND

The purpose of the meeting is to gain FDA agreement on the development program to support the approval of a 505 (b)(1) NDA for IDP-108 10% Solution for the treatment of onychomycosis of the toenails (b) (4)

2.0 DISCUSSION

Chemistry, Manufacturing and Controls (CMC)

Question 1:
The Sponsor has proposed release and stability specifications (section 3.2.3 and section 3.3.5.1) which it believes are adequate to establish the quality and stability of IDP-108 drug substance and drug product. The specifications will be finalized at the time of NDA submission based on additional stability data. Does the Agency agree?

Response:
No, we do not agree that the specifications are adequate for Phase 3 development. Please revise the drug product specification to include (1) USP<51> Antimicrobial Effectiveness Testing, and (2) limits for related substances.

Meeting Discussion:

The specification revisions should be implemented prior to initiation of the Phase 3 studies.

Question 2:
There are two noncompendial ingredients in IDP-108 Solution. Does the Agency agree with the proposed specifications for these ingredients (section 3.3.4.1)?

Response:
Yes, we agree with the proposed specifications for the two noncompendial ingredients for Phase 3 development. NDA specification is a review issue.

Additional Comments:
1. Please apply for an USAN name for the proposed drug substance. We recommend the inclusion of the USAN name in the NDA submission.

2. Your product contains a high percentage of alcohol. Therefore, flammability testing must be conducted in accordance with 16CFR 1500.43. If necessary, an appropriate flammability warning must be included in the product labeling.

3. We are unclear about the formulations used in clinical studies. Please provide a table correlating formulations to clinical and non-clinical studies.

4. Provide a representative sample for dosage form evaluation.

5. The design of the to-be-marketed container/closure system should be such that it can be easily differentiated from that of oral liquid dosage forms.

6. Please monitor weight loss and alcohol loss in the stability studies of drug product.

7. In Table 3.3.1.1 you indicate that cyclomethicone functions (b) (4) in the formulation. (b) (4) Please clarify your intent (b) (4) for cyclomethicone. If you don't (b) (4) provide a function for cyclomethicone (b) (4) (b) (4)

Meeting Discussion:

The sponsor does not intend (b) (4) for cyclomethicone.

Pharmacology/Toxicology

Question 3:
Does the Agency agree that the proposed nonclinical program (see section 4.1 for the nonclinical overview) is adequate to support approval of IDP-108 with an indication for the treatment of onychomycosis of the toenails (b) (4)

Response:
The proposed nonclinical program appears to be adequate. However, the completed nonclinical program will be a review issue. If new concerns arise, additional studies may be necessary.

You are reminded that the final study reports for the subcutaneous rat and rabbit embryofetal development studies should be submitted to the IND in adequate time for review prior to initiation of Phase 3 clinical studies.

Question 4:
An acceptable systemic route for the IDP-108 rat carcinogenicity study has not been identified although SC and oral administration have been thoroughly evaluated. Therefore, DPSI proposes (b) (4)

(b) (4) Is this approach acceptable?

Response:
No. Your proposal is not acceptable. A (b) (4) is not useful to support your nonclinical program. (b) (4) (b) (4) (b) (4) More appropriate criteria for dose selection for dermal carcinogenicity studies in rodents include the maximum feasible dose or the maximum tolerated dose.

Since you are currently conducting a dermal mouse carcinogenicity study with IDP-108, then the second carcinogenicity study should be conducted by a systemic route (i.e. oral or parenteral). However, based on the limited aqueous solubility of IDP-108 and the significant irritation produced by subcutaneous injection of IDP-108 in a propylene glycol vehicle, we are concerned that the vehicle may confound interpretation of the subcutaneous rat carcinogenicity study results and affect acceptability of the study. It might be acceptable for you to request a waiver for the conduct of a systemic carcinogenicity study with IDP-108. You should submit a justification for a waiver request to the IND. The waiver request should include all data concerning the different vehicles tested to solubilize IDP-108 with corresponding data that evaluated the tolerability of these different vehicles after subcutaneous administration to rats.

Question 5:
The Sponsor plans to initiate the rat carcinogenicity study as soon as possible, prior to the NDA submission. (b) (4) The mouse dermal carcinogenicity study report will be submitted with the NDA. The rat carcinogenicity report schedule for the NDA is based on (b) (4) (b) (4) (b) (4) Does the Agency agree with this rat carcinogenicity schedule?

Response:
No. (b) (4) (b) (4) All nonclinical carcinogenicity final study reports for a NME must be submitted with the NDA.

You are referred to the response provided to question 4 that discusses the possible waiver for a systemic rat carcinogenicity study.

Question 6:
Does the Agency agree a nonclinical photoirritation study does not need to be conducted since no absorption between 290 nm and 700 nm was noted in the UVB/UVA/VIS spectrum for the to-be-marketed formulation?

Response:
You may request a waiver for the conduct of a nonclinical photoirritation study with IDP-108. You should submit the UVB/UVA/VIS spectrum (290 – 700 nm) for IDP-108 to the IND with a waiver request for conduct of a nonclinical photoirritation study. However, if the clinical formulation changes, this may trigger the need for additional photo absorption analysis and conduct of a nonclinical photoirritation study.

Question 7:
IDP-108 Solution contains the ingredient C12-15 Alkyl Lactate. This ingredient is widely used in cosmetic products but is not on the IIG list. Two major components of C12-15 Alkyl Lactate, (b) (4) (b) (4) The dermal toxicity of C12-15 Alkyl Lactate has been effectively evaluated in the IDP-108 Solution chronic minipig toxicity in part, because of the large multiple between the human equivalent dose and the maximal clinical dose. DPSI proposes that no additional nonclinical studies are required for characterization of this ingredient. Does the Agency agree?

Response:
We agree that no additional nonclinical studies are needed to evaluate the C12-15 Alkyl Lactate excipient at this time. However, the final determination will be made after review of the 9 month dermal minipig study and the dermal mouse carcinogenicity study conducted with the IDP-108 formulation that contains the C12-15 Alkyl Lactate excipient.

Clinical Pharmacology/Biopharmaceutics

Question 8:
Systemic exposure after nail application of the maximal dose of IDP-108 Solution, 10% has been characterized in a Phase 1 PK study. Ten healthy volunteers repeatedly applied IDP-108 Solution, 0.425 mL/day for 7 consecutive days to all 10 toenails. Plasma levels of parent and H3 metabolite were analyzed with a validated LC/MS/MS method and PK parameters calculated. In addition, PK samples were collected in the Phase 2 study from 9 subjects in the IDP-108 Solution, 10% (non-occluded). PK sampling in the Phase 2 study was limited to a single sample (ca. 12 hours after nail application) collected at 4, 8, 12, 24, 36, and 40 weeks (30 day follow up). The plasma levels of parent and H3 metabolite from the Phase 2 study were also analyzed. Upon repeated administration, the T_{max} for IDP-108 and H3 were highly variable (0-24h range) and roughly averaged 10 and 8 hours, respectively, in the Phase 1 PK study. The Phase 1 PK plasma levels (and hence T_{max} values) were highly variable as is commonly seen with low or sub-nanogram/mL values after topical drug administration. Comparison of the average plasma levels of IDP-108 and H3 metabolite 12 hour after dosing from the Phase 1 and the average plasma concentrations across all sampling days from the Phase 2 study were quite similar, IDP-108: 0.36±0.20 vs 0.71±0.61 and H3: 1.35±0.62vs 1.60±1.15 ng/mL, respectively. These data show that long term treatment results in comparable systemic exposure as the maximum dosing in the Phase 1 7-day PK study.

Based on the clinical PK data developed for IDP-108 coupled with the negligible systemic exposure after topical nail application, DPSI does not believe that additional PK evaluation is needed. Does FDA agree?

Response:

No, the phase 1 study as indicated in the meeting package was conducted in healthy subjects with intact (non-inflamed) nails and surrounding tissues. The fact that plasma levels are detectable following application to normal intact tissues strongly indicates that the disrupted nail plates that are present in onychomycosis would lead to altered absorption and plasma levels. The results from the phase 2 study are somewhat inconclusive as the information contained in the meeting package suggests sub-maximal usage. The goal of the in vivo PK study program for a topically applied product is to evaluate the potential for drug absorption under a maximal usage paradigm in patients with diseased tissues.

It should also be noted that the PK sampling program employed in both studies was coarse in nature with multi-week intervals between samples.

The FDA recommends that a new protocol incorporating the best features of the previously conducted Phase 1 (full nail coverage) and Phase 2 (diseased tissues) be utilized. While reduced plasma sampling schedules have been used in topical drug development, they are more in the nature of surveillance pharmacokinetics when blood levels are not anticipated. Given that now we have a demonstration of in vivo absorption from two studies, a more robust PK sampling procedure would need to be employed.

Clinical/Biostatistics

Question 9:
The following clinical studies have been completed to support the approval for IDP-108 topical solution:

- Phase 1 21-day cumulative irritation study in 55 healthy volunteers (DPSIIDP-108-P1-01)
- Phase 1 Patch Test (irritation and photosensitization) Study in 28 healthy volunteers (KP-103-02)
- Phase 2 9-month Dose-ranging study in 135 patients with onychomycosis of the toenails (DPSI-IDP-108-P2-01)
- Phase 1 PK study in 10 healthy volunteers (DPSI-IDP-108-P1-02)

DSPI has submitted a waiver for a QT/QTc study (see serial submission 0015).

In addition, IDP-108 solution and components do not absorb between 290 and 700 nm. Therefore, we are requesting a waiver for the phototoxicity and photoallergy studies.

Our proposed plan is to conduct the following clinical studies with the to-be-marketed formulation:

- Phase 1 Human Repeat Insult Patch (irritation and sensitization) test study in 230-240 healthy volunteers
- Two 52-week (48 weeks of treatment with 4 week follow-up) Multi-center Phase 3 Safety and Efficacy Studies in patients with onychomycosis of the toenails (825 patients per study)

Does the Agency agree that the proposed clinical program is adequate to support approval of IDP-108 with an indication for the treatment of onychomycosis of the toenails due to dermatophytes?

Response:
Your proposed development plan appears adequate to meet NDA filing requirements; however, adequacy of the data and ultimate NDA approval are review issues. See additional comments that follow and included in this document.

Meeting Discussion:
The Agency strongly advised that a SPA be submitted, as no agreements were reached during the meeting regarding the protocol and statistical analysis plan.

Question 10:
The Phase 3 trials are large, with over 1000 patients exposed to topical IDP-108 daily for 48 weeks. Therefore the Sponsor believes that the requirements for long term safety will have been met, and does not plan to conduct a separate Long Term Safety study. Does the Agency agree?

Response:
Minimal data is available for safety evaluation. Provided that sufficient numbers of subjects are exposed for 6 months at dosage levels intended for clinical use(e.g., IDP-108 10% solution), and no adverse safety outcomes are observed, conduct of a separate Long Term Safety study may not be necessary. You are referred to ICH-E1A Guidance for Industry: the Extent of Population Exposure to Assess Clinical Safety.

Question 11:
The primary endpoint for the two Phase 3 clinical studies is complete cure at the 28 day post treatment follow up visit. Complete cure is defined (b) (4) (b) (4) Does Agency agree with the primary endpoint?

Response:
Your definition of clinical cure and mycologic cure should be clarified in establishing the primary endpoint for the two Phase 3 clinical studies. (b) (4) (b) (4) will reduce investigator interpretation (e.g., residual discoloration).

The Agency recommends that the primary endpoint, Complete Cure, be defined as follows:

- Clinical Cure, defined as zero% clinical involvement of the target nails (nails are totally clear),

in addition to

- Mycologic Cure, defined as negative KOH (potassium hydroxide) examination as well as negative culture of the target nail specimen.

Meeting Discussion:

The Agency recommends that the sponsor provide additional objective documentation of percent nail involvement at all clinical study sites (e.g., digital photographs of the target nails).

Question 12:
Does the Agency agree that the proposed study design for the two Phase 3 clinical studies (see **Appendix 1** for the complete clinical protocol) is adequate to support the NDA and approval of IDP-108?

Response:
You propose to conduct two multicenter, randomized, 2-arm, double-blind, vehicle-controlled, parallel-comparison study designed to assess the safety and efficacy of IDP-108 10% topical solution in subjects with mild to moderate onychomycosis of at least one great toenail confirmed by fungal culture of the toenail.

Successful completion of two 52-week, vehicle controlled studies with complete cure as the primary endpoint would support an NDA filing. The adequacy of the studies would be a review issue.

We have the following comments on Protocol DPSI-IDP-108-P3-01/02.

1. You have not provided justification that the studies are adequately powered (i.e. you have not provided the treatment effect estimates used in the calculation or why such estimates would be appropriate). If inaccurate estimates are used, the studies could be underpowered. We also note that no Phase 2 trials were conducted with the duration of therapy you intend for Phase 3 trials.
2. Provide additional details about how the investigator calculates the percent nail involvement. Accurate and consistent assessments by the investigators are needed to adequately evaluate efficacy.

Meeting Discussion:

The sponsor noted that they inadvertently omitted the statistical basis for their power calculation. They plan to include this information with their statistical analysis plan when submitted for review.

3. You have proposed the following secondary endpoints: clinical efficacy (<20% affected target nail area) at Week 52, mycological cure (negative KOH and culture) at Week 52, and the number of non-target nails affected at Week 52. In general the set of secondary

endpoints intended to support efficacy should be clinically relevant and adjusted for multiplicity.

4. Study drug application instructions should be clarified in the protocol.
5. You should submit your final Phase 3 protocols to the IND. It would be helpful if the final protocols were marked with highlight/strikeout to elucidate any changes from the versions of the protocols submitted for review for today's meeting.

Question 13:
DPSI submitted a waiver request for the QT/QTc study in serial submission 0015. Does the Agency agree with this waiver request?

Response:
You have submitted serial submission 0015 which is a request for a waiver to conduct a QT/QTc study. The Agency's response currently under review and is pending.

Question 14:
IDP-108 solution and components do not absorb between 290 and 700 nm (see section 3.3.6 for the UV/Visible absorption spectra). In accordance with the Guidance for Industry Photosafety Testing, DPSI is hereby requesting a waiver for conducting phototoxicity and photoallergy studies. Does the Agency agree?

Response:
Please identify whether the UV spectrum curve for the 10 % IDP 108 solution was obtained using the "final- to-be marketed" formulation. Also clarify whether the "modified/to-be-marketed" formulation listed on page 80 is the "final-to-be-marketed" formulation to be used in phase 1 Human Repeat Insult Patch (irritation and sensitization) test study and proposed phase 3 Safety and Efficacy Studies.

The UV absorption spectrum using the "final-to-be marketed" formulation and a waiver request from conduct of phototoxicity and photoallergenicity testing should be officially submitted by DSPI to the Agency under the IND. If UV spectrum data submitted in the Briefing Package does reflect the "final-to-be-marketed" formulation, then although the absorption does not appear to be zero, we concur that there is not significant absorption to warrant the conduct of dermal photosafety studies given the desired indication of toenail onychomycosis. Thus a waiver for phototoxicity and photoallergy studies at the time of NDA submission may be justified for the indication of toenail onychomycosis.

Question 15:
The total number of subjects exposed to the drug product after completion of the planned clinical studies will be (b) (4) as shown in the table below. This will meet the requirement of approximately 1500 subjects exposed the drug product as per ICH E1A. Does the agency agree?

Total Exposure		
Studies completed or in progress	Length of Exposure	# of subjects
P1 21 day Cumulative Irritation Study	21 days	(b) (4)
P1 Irritation and photosensitization Patch study (7 days) - currently in progress in Japan	7 days	
P2 DRF Study	9 months	
P1b 28 d PK exposure study - currently in progress in Japan	28 days	
P1 PK study	7 days	
Planned Studies		
P3 Safety and Efficacy Studies	11 months	
P1 RIPT Study	3 weeks	
TOTAL		

Response:
No, at this juncture the Agency does not agree that 1500 subjects will have been exposed to study drug as per ICH EIA. In addition to citing numbers needed, dosage and duration of exposure requirements are stipulated in the ICH-E1A Guideline for Industry.

Clinical Microbiology

Question 16:
The Sponsor plans is to conduct microbiological susceptibility studies on at least 100 total clinical isolates for the dermatophytes (T. rubrum and T. mentagrophytes) from broad geographic regions of the United States. Does the Agency agree with this approach?

Response:

You should submit, prior to conducting efficacy trials involving human subjects, in vitro data describing the activity of IDP-108 against target pathogens. This data should include at least 100 isolates of each pathogen that may be listed in the proposed indications for the antifungal. Tabulated reports should describe the MIC_{90} and MIC_{range} for IDP-108 and appropriate comparators against fungal pathogens. Tested isolates should be recently collected from clinical sources, and primarily collected in the U.S. (geographic origin, specimen source, and date of collection should be included in tabular presentations). Specific fungi may be sub-grouped by

susceptibility phenotype (e.g. azole-resistant *T. rubrum*). Additional pre-clinical information should include data from recent studies designed to investigate the development of resistance in dermatophytes to IDP-108, and studies designed to confirm the mechanism of antifungal action of IDP-108.

Dermatophyte isolates collected during efficacy studies should be tested by a central, appropriately accredited laboratory. Testing should include confirmation of identification to species level, and susceptibility testing collected at the Baseline Visit, EOT Visit, and TOC Visit. Susceptibility testing should conform to methods approved by the Clinical Laboratory and Standard Institute (CLSI 2008). All dermatophyte isolates collected during clinical trials should be preserved for additional testing, as necessary. You should submit the descriptions of procedures used for specimen collection, microscopic evaluation (KOH or calcofluor white prep), specimen transport, fungal identification, any molecular assays, prior to initiation of studies, and isolate preservation. This information should also include details of quality control procedures and quality control ranges used in susceptibility testing.

References:
Clinical and Laboratory Standards Institute (CLSI). *Reference Method for Broth Dilution Antifungal Susceptibility Testing of Filamentous Fungi: Approved Standard – Second Edition.* CLSI document M38-A2 (ISBN 1-56238-668-9). Clinical and Laboratory Standard Institute, 940 West Valley Road, Suite 1400, Wayne, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2008.

Additional Administrative Comments

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND might identify additional comments or information requests.

2. Please refer to the Guidance for Industry: Special Protocol Assessment and submit final protocol(s) to the IND for FDA review as a **REQUEST FOR SPECIAL PROTOCOL ASSESSMENT** (SPA). Please clearly identify this submission as an SPA in bolded block letters at the top of your cover letter. Also, the cover letter should clearly state the type of protocol being submitted (i.e., clinical or carcinogenicity) and include a reference to this End-of-Phase 2 meeting. Ten desk copies (or alternatively, an electronic copy) of this SPA should be submitted directly to the project manager.

3. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).

4. We remind you of the Pediatric Research Equity Act of 2007 which requires all applications for a new active ingredient, new dosage form, new indication, new route of administration, or new dosing regimen to contain an assessment of the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations unless this requirement is

waived or deferred.

5. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry: Qualifying for Pediatric Exclusivity for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

6. In response to a final rule published February 11, 1998, the regulations 21 CFR 314.50(d)(5)(v) and 314.50(d)(5)(vi)(a) were amended to require sponsors to present safety and effectiveness data "by gender, age, and racial subgroups" in an NDA. Therefore, as you are gathering your data and compiling your NDA, we request that you include this demographic analysis.

7. We remind you that effective June 30, 2006, all submissions must include content and format of prescribing information for human drug and biologic products based on the new Physicians Labeling Rule (see attached website http://www.fda.gov/cder/regulatory/physLabel/default.htm for additional details).

8. You are encouraged to request a Pre-NDA Meeting at the appropriate time. Your meeting briefing package should, at a minimum, include top-line Phase 3 clinical study results and questions regarding the content and format of your planned NDA.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
IND 77732	GI 1		IDP 108 (KP 103)
IND 77732	GI 1		IDP 108 (KP 103)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUSAN J WALKER
08/17/2009